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AN ADDRESS AT THE FORMAL OPENING OF THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH ON MAY 11, 1906.

By William H. Welch, M. D.

The support of hospitals has always made a strong appeal to the philanthropy of the State and of individual citizens, and the importance to the community of educated physicians has been appreciated, although in this country until recent years most inadequately, but the recognition of medical science as a rewarding object of public and private endowment is almost wholly the result of discoveries in this department of knowledge made during the last quarter of a century. An eloquent witness to the awakening of this enlightened and beneficent sentiment, is the establishment, in 1901, of the Rockefeller Institute for Medical Research with its laboratories formally opened to-day.

While the scientific study of infectious diseases is, of course, not of recent origin and had been pursued as a part of the functions of health departments and of university laboratories of hygiene and of pathology, the first provision of a special laboratory for this purpose was made by the German Government in 1880 in the Imperial Health Office in Berlin, and to the directorship of this laboratory was called from his country practice Robert Koch, who four years before had startled the scientific world by his memorable investigations of anthrax. The supremacy of Germany in science is due above all to its laboratories, and no more fruitful record of scientific discoveries within the same space of time can be found than that afforded by this laboratory during Koch's connection with it from 1880 to 1885. Thence issued in rapid succession the description of those technical procedures which constitute the foundation of practical bacteriology and have been the chief instruments of all subsequent discoveries in this field, the determination of correct principles and methods of disinfection, and the announcement of such epochal discoveries as the causative germs of tuberculosis—doubtless the greatest discovery in this domain—of typhoid fever, diphtheria, cholera, with careful study of their properties.

The leading representative, however, of the independent laboratory devoted to medical science is the Pasteur Institute in Paris founded in 1886 and opened in 1888. The circumstances which led to the foundation of this Institute made probably a stronger appeal to popular sympathy and support than any others which have ever occurred in the history of medicine.

There stood in the first place the personality and the work of that great genius, Louis Pasteur, of noble and lovable character, one of the greatest benefactors of his kind the world has known, who for forty years had been engaged, often under adverse conditions, in investigations which combined the highest scientific interest with important industrial and humanitarian applications. Pasteur's revelation of the world of microscopic organisms in our environment—the air, the water and the soil—and his demonstration of their relation to the processes of fermentation and putrefaction had led Lister in the late sixties, even before anything was definitely known of the causative agency of bacteria in human diseases, to make the first and most important application of bacteriology to the prevention of disease by the introduction of the principles of antiseptic surgery, whereby untold thousands of human lives have been saved.

In 1880 came the most momentous of Pasteur's contributions to medical science and art in the introduction of the method of active immunization by the use of the living parasites of the disease attenuated in virulence, a method which until this date had remained without further application since its employment by Edward Jenner in 1796 in vaccinating against smallpox. Pasteur's researches in this field of immunity, marvelous in their originality, ingenuity and fertility of resource, culminated in 1885 in the announcement of his successful method of protective inoculation against that dread disease, rabies, and most of those here present will recall the enthusiasm with which this great triumph of experimental medicine was hailed throughout the civilized world.

It was under the immediate impression and the incentive of this discovery and as a mark of gratitude to Pasteur that over two and one-half million francs were raised within a short time by international subscription for the construction and endowment of an institute to bear his name, where the Pasteur treatment was to be carried out and ample facilities afforded for investigations of microorganisms and the problems of infectious diseases. This model Institute, much enlarged since its foundation and after the death of Pasteur under the directorship of Duclaux and now of Roux and, in one of its most important divisions, of Metchnikoff, has been a fruitful center of productive research and through its contributions to knowledge affords a signal illustration of the benefits to science and to humanity of the endowment of laboratories for the advancement of medical science.

It was under much the same influences that the important Imperial Institute for Experimental Medicine in St. Petersburg, with even wider scope than the Pasteur Institute, was founded and munificently endowed by Prince Alexander of Oldenburg in 1890.

In the following year the Prussian government established in Berlin under the directorship of Professor Koch the admirably organized and equipped Institute for Infectious Diseases, to which is attached, as to the Pasteur Institute, a hospital for infectious diseases. This and the excellent Institute for Experimental Therapeutics in Frankfort, under Professor Ehrlich's direction, founded also by the Prussian government in 1896, are unsurpassed in their scientific activities and in the number and value of their contributions to our knowledge of infection and immunity.

In 1891 was founded in London the British, later the Jenner, and now the Lister Institute of Preventive Medicine designed to be a national institute similar in character and purpose to the Institut Pasteur in Paris. The funds were contributed by the public and subsequently increased by Lord Iveagh's generous gift of two hundred and fifty thousand pounds.

Within less than a year after the foundation of the Rockefeller Institute for Medical Research the Memorial Institute for Infectious Diseases was founded in Chicago by Mr. and Mrs. Harold F. McCormick, and placed under the capable direction of Professor Hektoen.

The Institute for the Study, Treatment, and Prevention of Tuberculosis which bears the name of its beneficent founder, Henry Phipps, was incorporated in Philadelphia in 1903, and, while devoted to a single disease, it must be ranked among those of wide scope, when we consider the magnitude and surpassing importance of the problems pertaining to this disease.

It may also be noted that the Carnegie Institution in Washington, with its unequalled endowment of ten million dollars, includes within its scope the support of biological and chemical investigations of great importance to medical science, so that our country now stands in line with Germany, France and Great Britain in the opportunities afforded for research in medical and other sciences.

These various institutions have been mentioned as typifying the general aims and character of the Rockefeller Institute for Medical Research rather than to afford any complete picture of the material aid now available for the advancement of scientific medicine. If the latter were the purpose it would be necessary to travel far afield so as to include independent medical laboratories of more restricted scope, such as those for the study of cancer, the laboratories connected with departments of health, so well exemplified in our own country by those of the State Board of Health of Massachusetts and of the Department of Health of the City of New York, hospitals and the laboratories connected with them, the medical laboratories of universities and medical schools, such as the Thompson Yates and Johnston laboratories in Liverpool and the splendid new laboratories of the Harvard Medical School, laboratories established in recent years for the study of tropical diseases, such as our government laboratories in Manila, and funds available for special grants to investigators.

Impressive and encouraging as is this remarkable growth within recent years of laboratories devoted to the medical

sciences no one who has any knowledge of the vast field to be covered, of the difficulty and complexity of the problems, of the expenditure of money required, and of the returns in increased knowledge and benefits to mankind which have been attained and which may be expected in increasing measure, can for a moment suppose that the existing opportunities, considerable as they are, are adequate to meet the present and the future needs of scientific medicine.

As I have already stated, the wider recognition of medical science as a rewarding object of endowment is a result of discoveries made during the last quarter of a century, and it is of interest to inquire why this increased knowledge should have borne such abundant fruit. The result is not due to any change in the ultimate aims of medicine, which have always been what they are to-day and will remain—the prevention and the cure of disease, nor to the application to the solution of medical problems of any higher intellectual ability and skill than were possessed by physicians of past generations, nor to the growth of the scientific spirit, nor to the mere fact of a great scientific advance in medicine, for the most important contribution ever made to our understanding of the processes of disease was the discovery by Virchow in the middle of the last century of the principles and facts of cellular pathology, the foundation of modern pathology.

The awakening of this wider public interest in scientific medicine is attributable mainly to the opening of new paths of investigation which have led to a deeper and more helpful insight into the nature and the modes of prevention of a group of diseases—the infectious diseases—which stand in a more definite and intimate relation to the social, moral and physical well-being of mankind than any other class of diseases. The problems of infection which have been solved and kindred ones which give promise of solution are among the most important relating to human society. The dangers arising from the spread of contagious and other infectious diseases threaten not the individual only but industrial life and the whole fabric of modern society. Not medicine only but all the forces of society are needed to combat these dangers, and the agencies which furnish the knowledge and the weapons for this warfare are among the most powerful for the improvement of human society.

Great as was the material, intellectual and social progress of the world during the past century there is no advance which compares in its influence upon the happiness of mankind with the increased power to lessen physical suffering from disease and accident and to control the spread of pestilential diseases. Were we to-day as helpless as the physicians of past centuries in the face of plague, smallpox, typhus fever, cholera, yellow fever and other epidemic diseases, even if the existence of our modern crowded cities were possible, which may be doubted, the people would sit continually in the shadow of death. Great industrial activities of modern times, efforts to colonize and to reclaim for civilization vast tropical regions, the immense undertaking to construct the Panama canal, are all in the first instance dependent upon the successful application to sanitary problems of knowledge, much of it gained in recent years, concerning the causation and propagation of epidemic and endemic diseases.

And yet probably a fair measure of the general realization of these facts is the provision by Congress that of the seven members of the Isthmian Canal Commission four shall be engineers, without a word concerning a sanitarian on the commission. There could hardly be a more impressive opportunity to demonstrate to the world the practical value of our new knowledge concerning the mode of conveyance of malaria and yellow fever, the two great scourges of Panama, than that afforded by the digging of the Isthmian canal. The sanitary problem is not surpassed in difficulty by the engineering problem, but we may feel reasonable assurance that with the sanitary control in hands as trained and capable as those of Colonel Gorgas the ghastly experiences of the old French Panama Canal Company and in the construction of the railway will not be repeated.

To comprehend fully the degree and the character of the progress of modern medicine requires a kind of knowledge and a breadth of vision not possessed by the average man. He is concerned mainly with the prompt relief of his own ailments or those of his family. Of the triumphs of preventive medicine he knows little or nothing. With such dull matters as the decline in the death rate by one-half and the increase in the expectation of life by ten or twelve years during the last century he does not concern himself. He takes no account of the many perils which have been removed from his pathway since his birth, and indeed at the time of his birth, nor does he know that had he lived a little over a century ago and survived these perils he would probably be marked with smallpox.

While it is true that in the relief of physical suffering and in the treatment of disease and accident the progress has been great and the physician and the surgeon can do more, far more to-day than was possible to his predecessors, and while improvement in this direction must always be a chief aim of medicine, still it is in the prevention of disease that the most brilliant advances have been made. The one line of progress, that with which the daily work of the physician is concerned, affects the individual, the unit, the other, like all the greater movements in evolution, affects the race. It has been argued with a certain measure of plausibility that the interference with the law of the survival of the fittest assumed to be a result of the success of preventive medicine will bring about deterioration of the race. I believe the argument to be fallacious and that we already have sufficient experience to show that there need be no serious apprehension of such a result.

Before some accurate knowledge of the causation of infectious diseases was secured preventive medicine was a blundering science, not, however, without its one great victory of vaccination against smallpox, whereby one of the greatest scourges of mankind can be controlled and could be eradicated, if the measure were universally and efficiently applied. The establishment upon a firm foundation of the germ doctrine of infectious diseases, the discovery of the parasitic organisms of many of these diseases, the determination by experiment of

the mode of spread of certain others, and the experimental studies of infection and immunity have transformed the face of modern medicine.

The recognition, the forecasting, the comprehension of the symptoms and lesions, the treatment of a large number of infectious diseases have all been illuminated and furthered, but the boon of supreme import to the human race has been the lesson that these diseases are preventable.

Typhus fever, once widespread and of all diseases the most dependent upon filth and overcrowding, has fled to obscure, unsanitary corners of the world before the face of modern sanitation.

In consequence of the knowledge gained by Robert Koch and his co-workers Asiatic cholera, to the modern world the great representative of a devastating epidemic, will never again pursue its periodical, pandemic journeys around the world, even should it make the start.

Of bubonic plague, the most dreaded of all pestilences, which disappeared mysteriously from the civilized world over two centuries ago, we know the germ and the manner of propagation, and, although it has ravaged India for the last ten years with appalling severity, it can be and has been arrested in its spread when suitable measures of prevention are promptly applied.

Typhoid fever, the most important index of the general sanitary conditions of towns and cities, has been made practically to disappear from a number of cities where it formerly prevailed. That this disease is still so prevalent in many rural and urban districts of this country is due to a disgraceful neglect of well-known measures of sanitation.

To Major Walter Reed and his colleagues of the Army Commission this country and our neighbors to the south owe an inestimable debt of gratitude for the discovery of the mode of conveyance of yellow fever by a species of mosquito. On the basis of this knowledge the disease, which had been long such a menace to lives and commercial interests in our Southern States, has been eradicated from Cuba and can be controlled elsewhere.

Another army surgeon, Major Ross, acting upon the suggestion of Sir Patrick Manson, had previously demonstrated a similar mode of incubation and transportation of the parasite of malaria, discovered by Laveran, and it is now possible to attack intelligently and in many localities, as has already been proven, with good promise of success, the serious problem of checking or even eradicating a disease which renders many parts of the world almost uninhabitable by the Caucasian race and, even where less severe, hinders, as does no other disease, intellectual and industrial activities of the inhabitants. It is gratifying that one of our countrymen and a member of the Board of Directors of this Institute, Dr. Theobald Smith, by his investigations of Texas Cattle Fever, led the way in the discovery of the propagation of this class of disease through an insect host.

The deepest impress which has been made upon the average death rate of cities has been in the reduction of infant mortality through a better understanding of its causes. The Rockefeller Institute by the investigations which it has supported of the question of clean milk and of the causes of the summer diarrhœas of infants has already made important contributions to this subject, which have borne good fruit in this city and elsewhere.

No outcome of the modern science of bacteriology has made a more profound impression upon the medical profession and the public, or comes into closer relation to medical practice than Behring's discovery of the treatment of diphtheria by antitoxic serum, whereby in the last twelve years the mortality from this disease has been reduced to nearly one-fifth of the former rate.

The most stupendous task to which the medical profession has ever put its hands is the crusade against tuberculosis, whose preeminence as the leading cause of death in all communities is already threatened. Sufficient knowledge of the causation and mode of spread of this disease has been gained within the last quarter of a century to bring within the possible bounds of realization the hopes of even the most enthusiastic, but it will require a long time, much patience and a combination of all the forces of society, medical, legislative, educational, philanthropic, sociological, to attain this goal.

Time forbids further rehearsal even in this meagre and fragmentary fashion of the victories of preventive medicine. Enough has been said to make clear that man's power over disease has been greatly increased in these latter days. But great and rapid as the progress has been, it is small in comparison with what remains to be done. The new fields which have been opened have been explored only in relatively small part. There still remain important infectious diseases whose secrets have not been unlocked. Even with some whose causative agents are known, notably pneumonia and other acute respiratory affections and epidemic meningitis, very little has yet been achieved by way of prevention. The domain of artificial immunity and of the treatment of infections by specific sera and vaccines, so auspiciously opened by Pasteur and by Behring, is still full of difficult problems the solution of which may be of immense service in the warfare against disease. Of the cause of cancer and other malignant tumors nothing is known, although many workers with considerable resources at their disposal are engaged in its study. With the change in the incidence of disease, due at least in large part to the repression of the infections of early life, increased importance attaches to the study of the circulatory, renal and nervous diseases of later life, of whose underlying causes we are very imperfectly informed. There are and will arise medical problems enough of supreme importance to inspire workers for generations to come and to make demands upon all available resources.

In directing attention, as I have done, to some of the practical results of scientific discovery in medicine and in indicating certain of the important problems awaiting solution there is always the danger of giving to those unfamiliar with the methods and history of such discovery a false impression

of the way in which progress in scientific knowledge has been secured and is to be expected. The final victory is rarely the result of an immediate and direct onslaught upon the position ultimately secured. The advance has been by many and devious and gradual steps, leading often, it might appear, in quite different directions, and mounted more frequently than not to secure a wider prospect, but without any thought of the final goal. The army contains a multitude of recruits drawn from the most various fields, the biologist, the chemist, the physiologist contributing their share to medical triumphs just as truly as the pathologist, the bacteriologist, the hygienist, the clinician. The inspiration has been the search for truth and joy in the search far more than any utilitarian motive. In the fullness of time comes the great achievement; the leader is hailed, but he stands upon the shoulders of a multitude of predecessors whose contributions to the result are often lost from view.

In full recognition of the dependence of success in the warfare with disease upon increase of knowledge the Rockefeller Institute for Medical Research was founded by the enlightened munificence of Mr. John D. Rockefeller, to whom we make grateful acknowledgment. Likewise to the broad sympathies and active interest of his son, Mr. John D. Rockefeller, Jr., the origin and development of this institute are largely indebted.

What has already been accomplished, as well as the general scope and aims of the Institute have been concisely indicated to you by Dr. Holt. My purpose has been to show, although of necessity most inadequately, that these aims relate to matters of the highest significance to human society, that the present state of medical science and art requires large resources for its advancement, and that the returns in benefits to mankind have been and will continue to be great out of all proportion to the money expended. May the hopes of the founder and of those who have planned this Institute be abundantly fulfilled! May it contribute largely to the advancement of knowledge, and may the streams of knowledge which flow from it be " for the healing of the nations."

ON THE TEACHING OF PATHOLOGICAL PHYSIOLOGY.

By W. G. MacCallum, M. D.,

Associate Professor of Pathology, The Johns Hopkins University, Baltimore, Md.

The following outline of the course in pathological physiology recently begun at the Johns Hopkins University is intended to show the plan and aims of this work and to argue its importance in the general scheme of medical education. Heretofore, courses in pathology have concerned themselves chiefly if not exclusively with the study of pathological anatomy, practical demonstrations of the lesions met with at autopsy being varied here and there, by didactic lectures upon the underlying principles involved and the nature of the mechanical and chemical processes at work. As far as the practical work—that is the intimate contact of the student with real objects, is concerned, such courses are purely morphological and deal with the end results of the processes mentioned in the lectures. With these processes in action the student gains no direct acquaintance until he reaches the later years of his medical course when he is introduced into the wards and allowed to study the patients clinically. Then, it is true, he directly observes the altered functions of diseased organs but, as it were, at a distance. He may not apply other than clinical methods to these patients, such as auscultation and percussion, although it is clear that of recent years the perfection of the methods of clinical investigation approaches more and more closely that of the physiological laboratory. The fact, however, that he is dealing with a fellow human being, and that a suffering one, will necessarily limit greatly in many if not in all instances, the thoroughness and completeness of his application of these methods. Many of the most instructive of the precise methods at the command of the physiologist are not applicable to human beings at all, or if so, only indirectly, and by means of apparatus much less delicate and exact than that commonly used in the laboratory.

Further, it is well known that unless special care is taken to avoid such a thing the student is likely to complete his study of pathological anatomy before he begins his clinical work, and he is in the position then of trying in each clinical case to correlate sometimes faintly remembered anatomical changes with the signs and symptoms which he now finds before him. It was for these reasons that it seemed desirable to teach pathology, not merely from the morphological standpoint, but more particularly to bring clearly before the student the alterations in function which result from disease, by applying to the organs in the course of their reaction to experimentally produced lesions, all of the exact methods of the physiologist. By this means, always in association with anatomical studies, it is possible to correlate in the mind of the student much more closely than otherwise the changes in function and the anatomical alteration.

In this study of disturbed function it was planned to produce experimentally such lesions of the various organs as are commonly met with in the wards, and any available methods were used to this end. It may be remarked in passing that ideal uncomplicated lesions may be produced in this way which will illustrate the principle involved often in a way seldom seen in clinical cases.

Facilities for the prosecution of this work were afforded in

the new Hunterian Laboratory for Experimental Medicine which the trustees of the University have generously erected for such purposes. Of this building, Dr. Cushing has already written a description in which he details the arrangements for the accommodation of animals in the whole basement, and the operative work which is carried on for and by the students in one-half of the upper floor. The other half of that floor is devoted to experimental pathology and is divided into several small rooms provided with the necessary apparatus. Fig. 1 shows the general arrangement of one of these rooms, in which a skylight furnishes a particularly advantageous illumination.

In planning a course in pathological physiology it immediately became obvious that the whole field could not be covered even in the most superficial way within the portion of the academic year at our disposal, and it was therefore decided to subdivide the course, taking up the diseases of a different set of organs each year. Thus the course already given, which lasted about two months with the three afternoon exercises a week, was devoted entirely to the circulatory system, while next year it is proposed to study in a similar way the diseases of the organs of internal secretion and so on.

In a general way the lectures of Cohnheim formed a model for this course, the experiments described there being actually carried out. It was not thought desirable, however, to limit the course to experimental work, but certain days were devoted to the study of the gross and microscopical anatomy of the lesions to be studied experimentally, as exemplified by specimens in the museum, etc. Thus the course was actually a course in the general pathology of the circulatory system.

Diseases of the pericardium were first taken up and studied anatomically, especially with regard to the nature and quantity of the exudate and its position with reference to the heart. These being the factors of especial importance in affecting the function of the heart, the experimental study was designed as described by Cohnheim, to render clear the effects upon the circulation produced by such an exudate imitated by the introduction of fluid under pressure into the pericardium. The apparatus was so arranged that fluid might be introduced or withdrawn at will and the pressure correspondingly changed. The effect of rather rapid distension of the pericardium with fluid is shown in Curve 1, in which it is seen that the arterial pressure rapidly sinks to a minimum, the pulsation disappearing in time. The pressure in the pulmonary artery (green) is also lowered and the pulsation obliterated, while in the innominate vein (blue) the pressure is elevated slightly. The death of the animal would rapidly ensue if this distension of the pericardium thus suddenly produced were maintained, but the pressures return to normal and pulsation reappears when it is withdrawn. When the exudate appears gradually, as it usually does, the heart is able to tolerate the pressure of much larger amounts. Evidently its power of dilating actively is called into play there.

Anatomical study of various acute and chronic lesions of the endocardium and especially of the heart valves with the resulting changes in the heart and circulation was followed by the experimental study of these lesions, nearly all of which can be reproduced by various methods. Exact records of pulsation and pressure could then be taken from any portion of the circulatory system, such as the pulmonary arteries and veins, or the chambers of the heart, although these are entirely inaccessible to the clinician. Such records have been produced systematically by von Basch, Moritz, and others by the aid of ingeniously constructed models of the circulation made of glass and rubber, and fitted with valves to imitate the actual conditions, but nervous and muscular control is lacking in these models and one feels sure that the reaction of such a model to the production of an obstruction or insufficiency of one of its valves must differ frequently in unsuspected ways from the reaction of the living animal with its wonderful adaptive mechanisms. Nevertheless, they are able to produce curves which show fairly well the mechanism of the various alterations. Rosenbach, Kornfeld, Bettelheim, Kauders, and several others have studied quite extensively, some of these lesions experimentally produced in animals with their results, and Klebs and others have constructed special instruments to produce tears in the more inaccessible valves.

During this course we were able to study various degrees of insufficiency and stenosis of each of the valves recording before and after the production of the lesion the pulsation and pressures in different parts of the circulation. By methods which will be described elsewhere similar valvular lesions were produced without exposing the heart, and the animals kept for a time to determine the effect upon the heart, but in the experiments of the course it was found desirable to expose the circulatory apparatus so that students might directly observe the changes in the size of the heart and in the character of its contractions and further might listen to the murmurs by applying the bell of the stethoscope directly to the wall of the heart and to the large blood-vessels. For this purpose a stethoscope was constructed with a very small bell, by the aid of which murmurs could be traced along the vessels and localized on various points over the heart wall as will be described in a separate paper.

The nature of the alterations in the pulse could also be recorded by the use of a tambour attached to the leaden tube leading from the canula in an artery, this being necessary from the fact that the ordinary mercury manometer does not record exactly slight variations in the character of the pulse.

The lesions were produced in various ways. Insufficiency of the valves was brought about by tearing them, either in the case of the aortic valves by the method of Rosenbach, which consists in inserting a blunt probe through the carotid and rupturing the valve, or in the case of the mitral or tricuspid by the insertion of a blunt hook with inner cutting edge (Fig. 2) through the vein, or preferably through the auricular appendage, which could then be tied off after removal of the hook. It was found that such a hook was also very serviceable instead of the probe in tearing the aortic valves, for after being pushed through the base of a segment it could then be

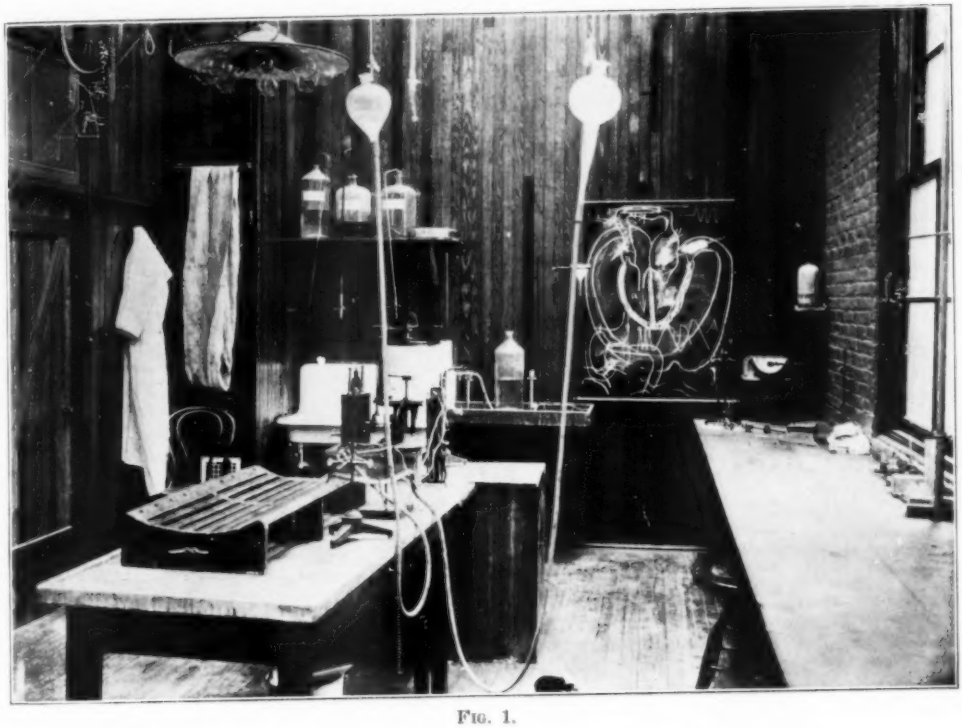
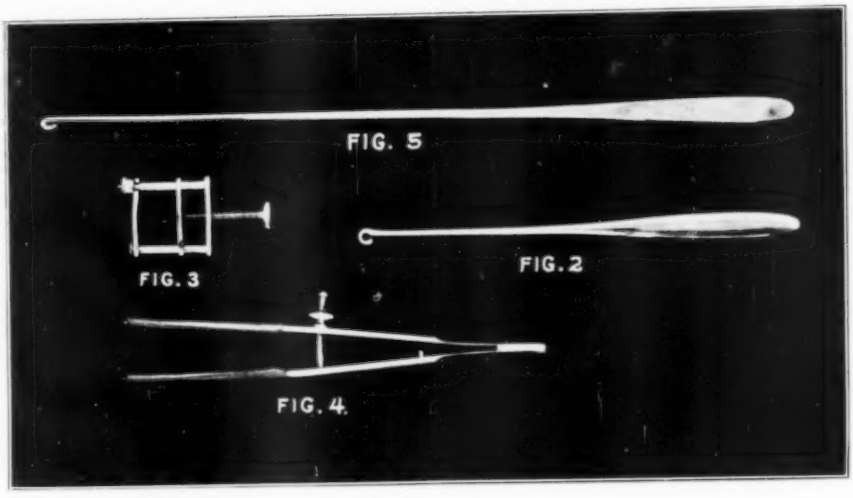
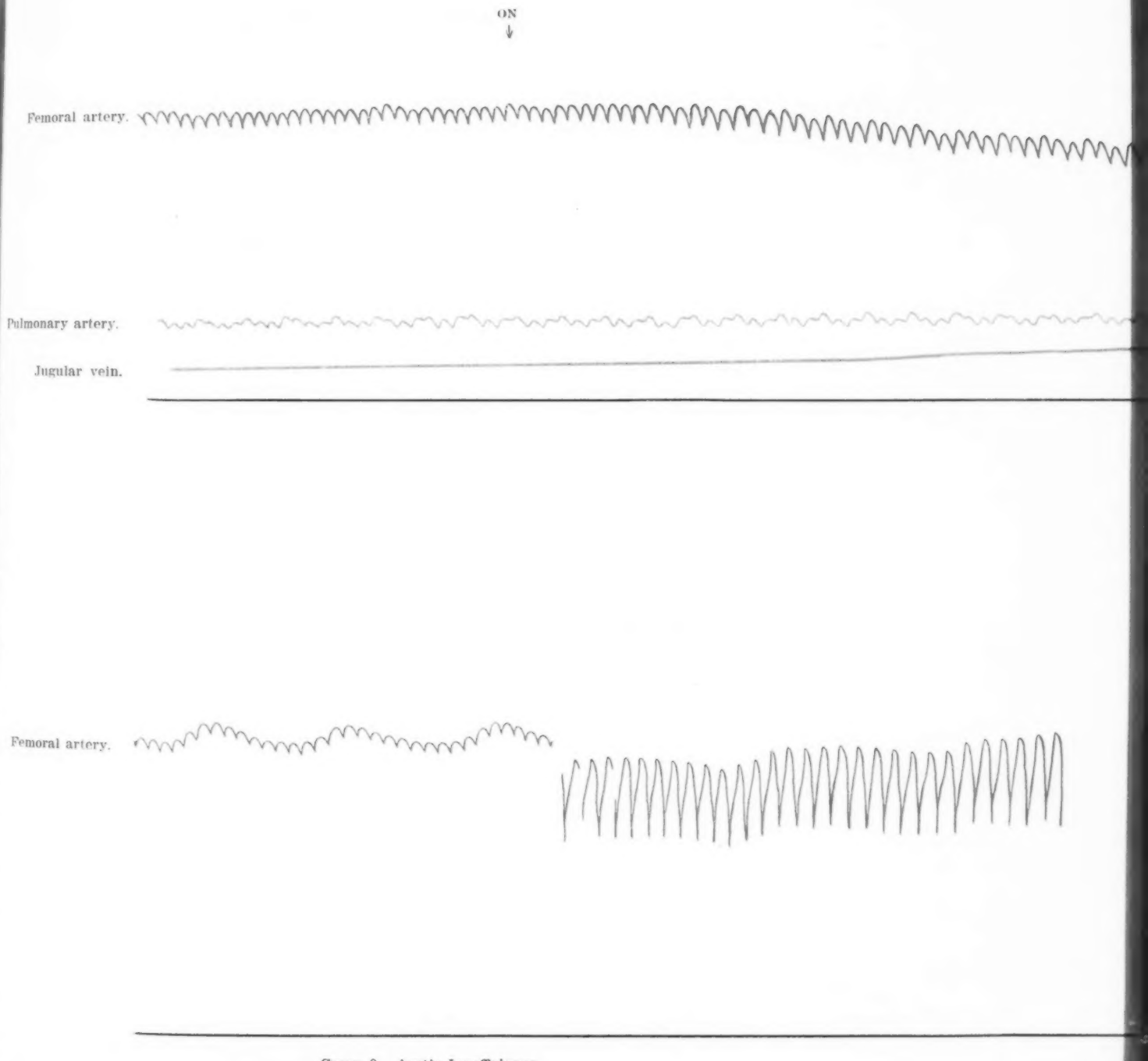
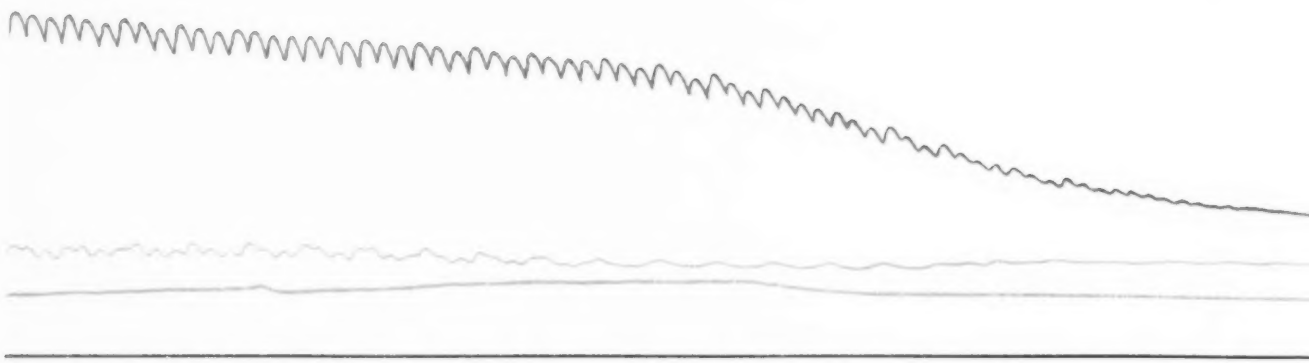


FIG. 1.

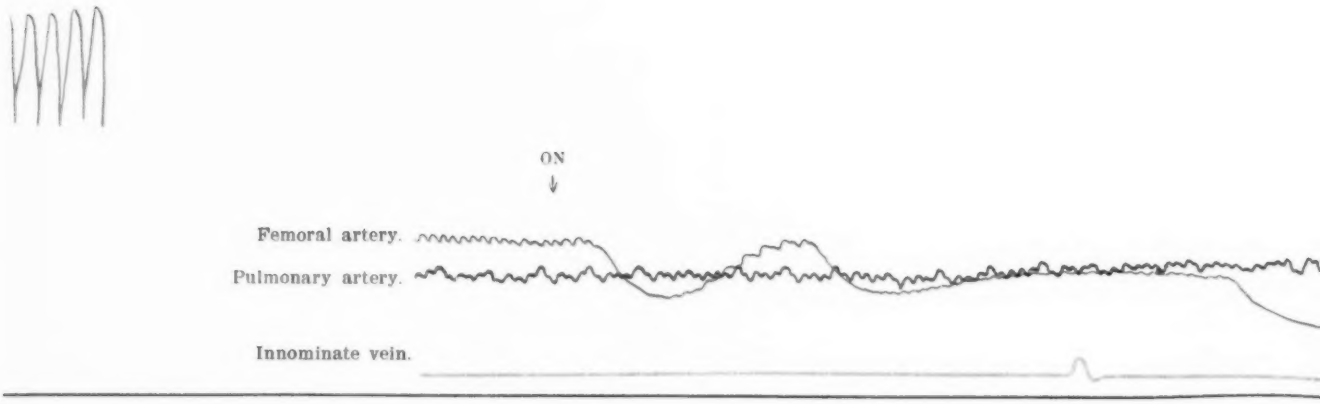


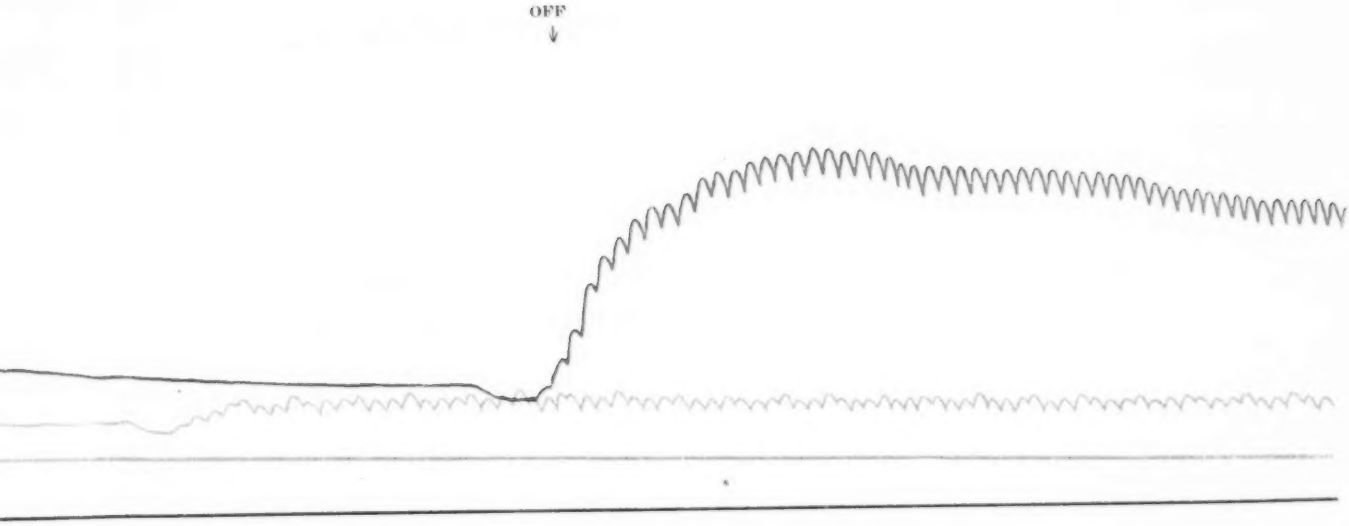


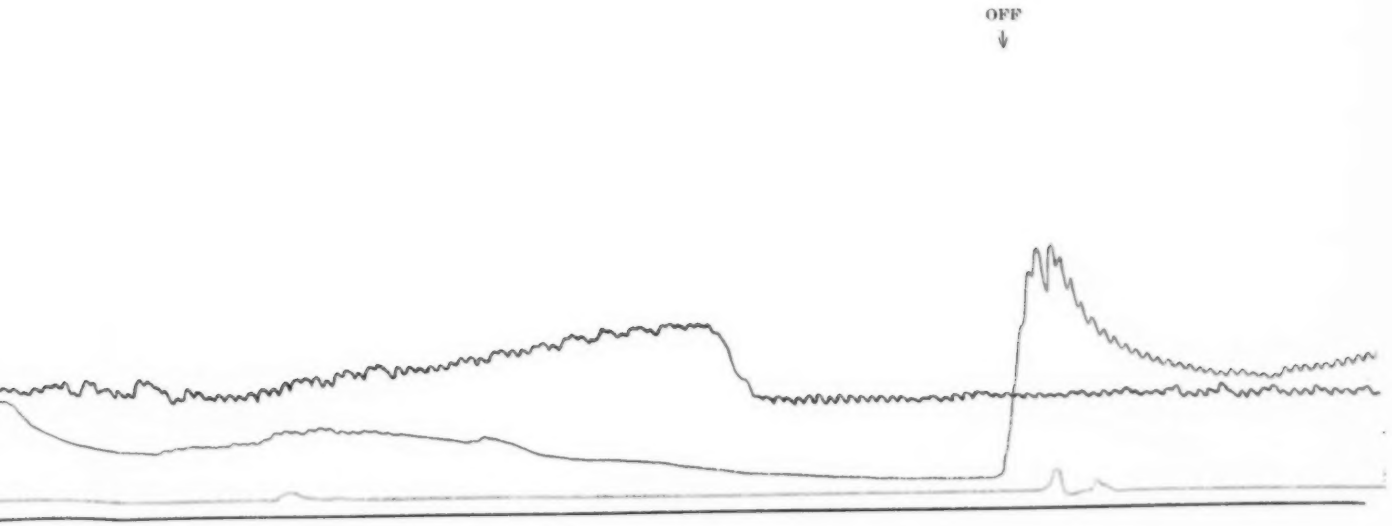
Curve 2. Aortic Insufficiency.



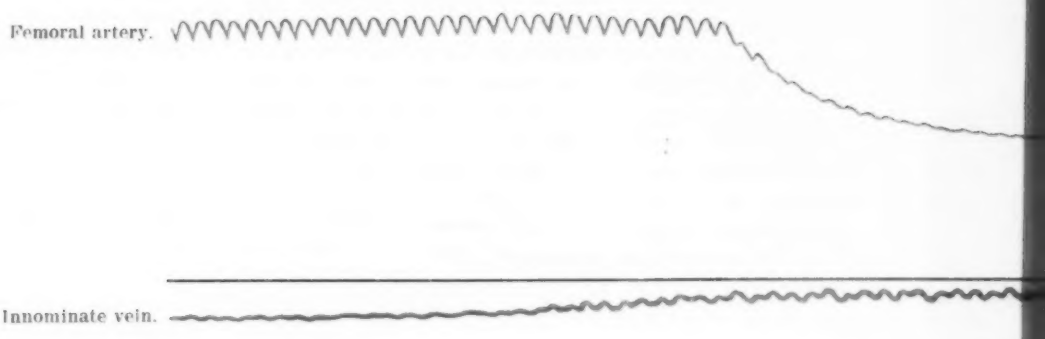
Curve 1. Pericardial effusion.



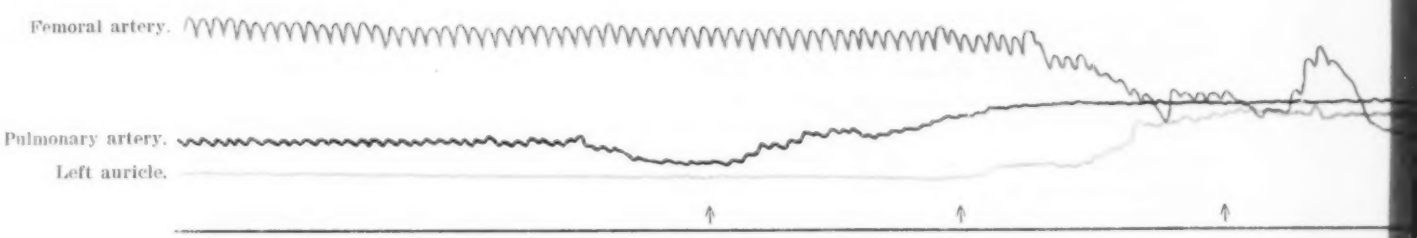




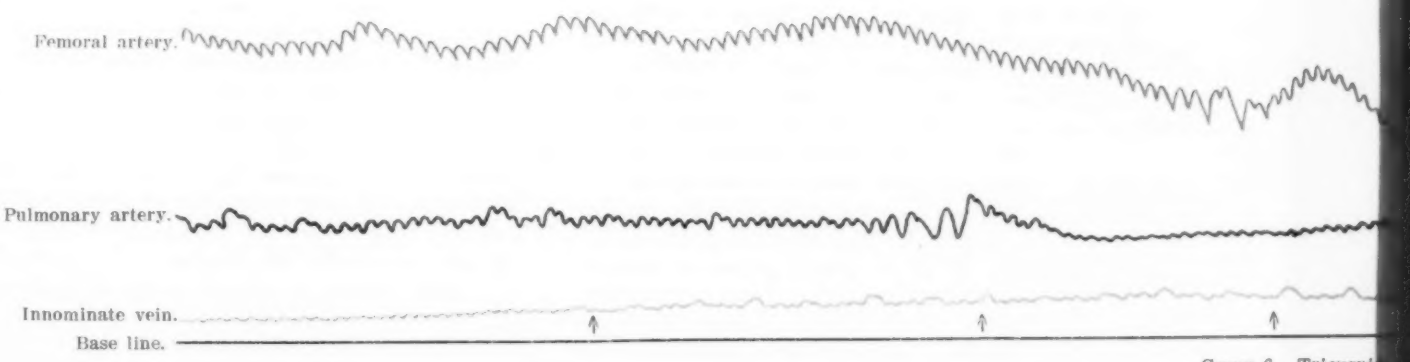
Curve 3. Aortic Stenosis.



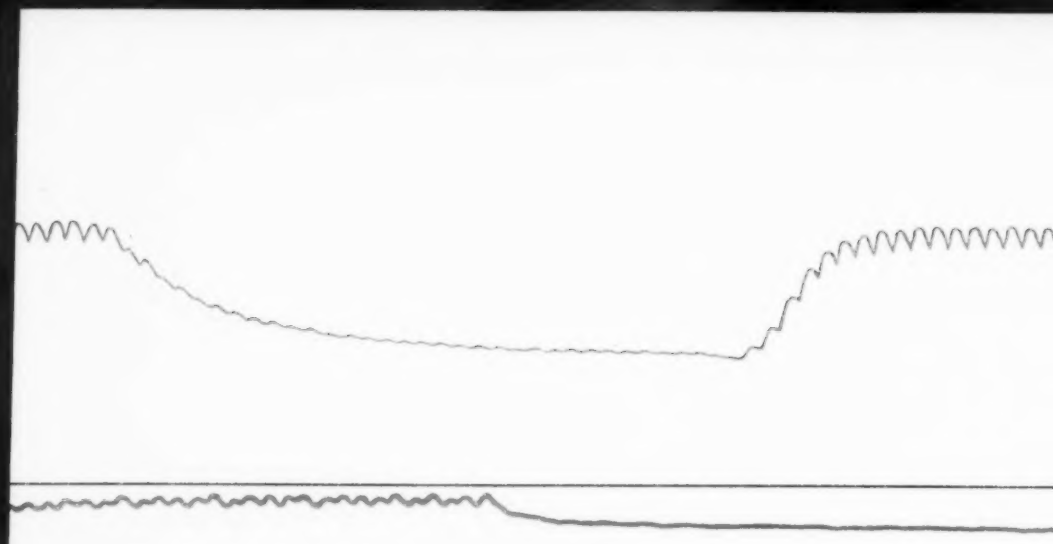
Curve 4. Pulmon



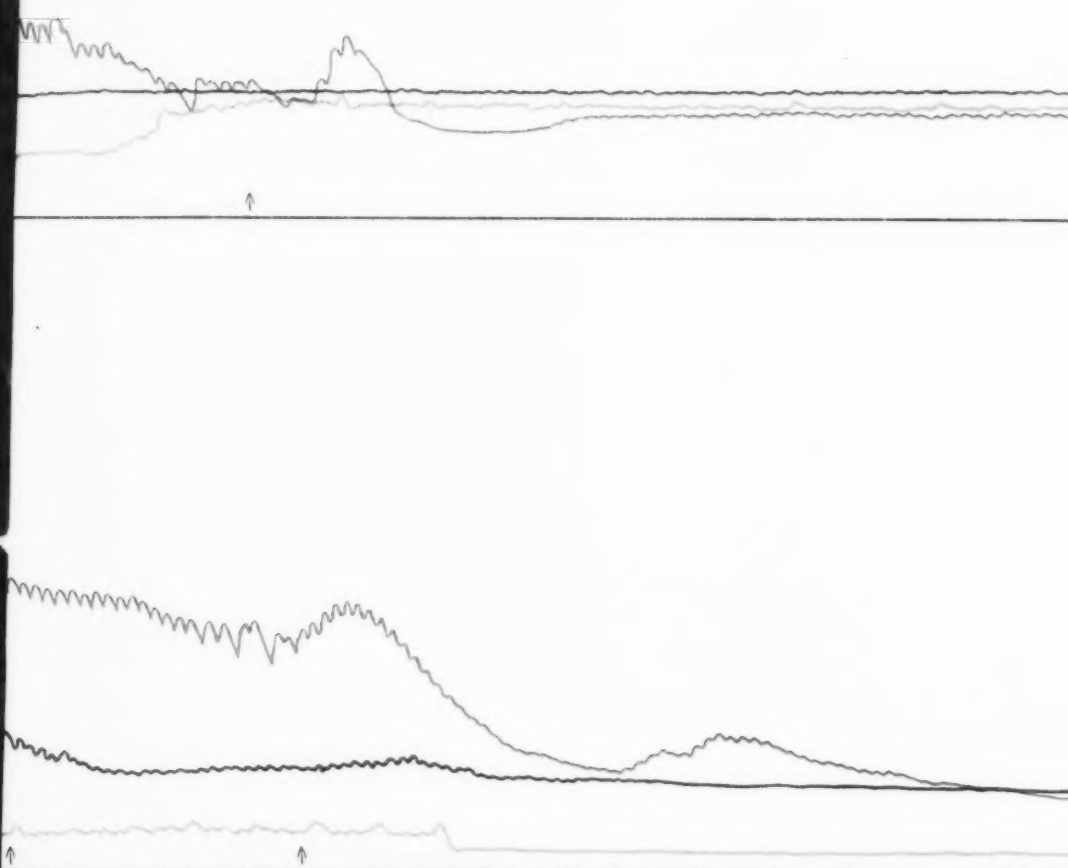
Curve 5. Mitral Stenosis.



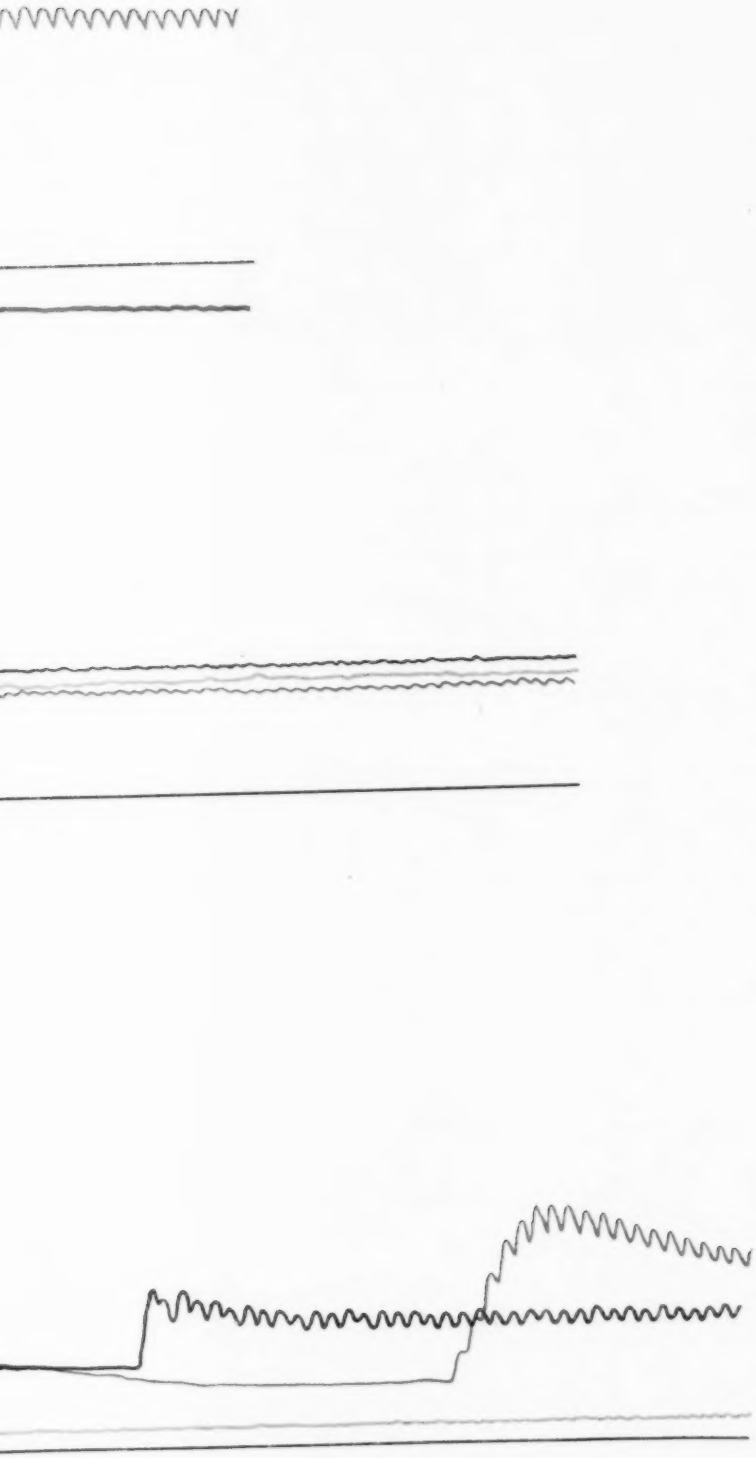
Curve 6. Tricuspi



Curve 4. Pulmonary Stenosis.



Curve 6. Tricuspid Stenosis.



turned toward the lumen and would cut the valve cleanly on its return. Stenosis of the arterial orifices was easily produced by the application of a screw clamp with one movable limb (Fig. 3) by means of which any degree of constriction could be brought about. In the case of the mitral and tricuspid orifices a clamp of the form shown in Fig. 4, with the ends guarded with rubber tubes, could be applied and constriction produced by means of the screw in the center. It was also found possible to attain almost the same result by passing a suture with a long curved needle through the heart about the mitral ring and drawing it tight, but this method is less easy.

Aortic insufficiency was first studied and the remarkable maintenance of arterial blood pressure with peculiar collapsing pulse shown in a curve (Curve 2). A loud diastolic murmur could be heard over the heart and to some extent along the vessels. Even in the smaller arteries far from the heart a pistol-shot clap could be heard with the stethoscope.

Aortic stenosis produced the effects upon arterial and venous pressure, shown in Curve 3, the line recording venous pressure showing but little change, while that from the pulmonary artery shows the gradual rise in pressure in the pulmonary circulation. A harsh thrill could be felt beyond the clamp by placing the finger upon the arch of the aorta and this was associated with a loud murmur best heard along the aortic arch.

Stenosis of the pulmonary artery similarly produced (Curve 4) has a somewhat similar effect but brings about a much greater elevation of the general venous pressure.

Mitral insufficiency was studied in detail and the phenomena associated with it are described in a separate paper. It was found easy to reach through the left auricular appendage and cut the valve with the knife hook figured above, while manometers were connected with several parts of the circulation. Briefly it was found in these rapidly produced and excessive lesions that the arterial pressure sinks at once, while the pressure in the pulmonary circulation is affected by the addition of the regurgitant amount, by the diminution in blood supply owing to the incomplete expulsion from the left ventricle, and by the communication of a more or less violent backward pulsation to the pulmonary stream of blood. It is necessary to take into account all of these factors in explaining the hypertrophy of the right ventricle. Since it is so rare to find an entirely uncomplicated mitral insufficiency in human beings and to observe its exact and unaided influence in producing cardiac hypertrophies it has been thought interesting to tear the valves by a long knife hook (Fig. 5) introduced along the carotid and between the aortic valves; on its return the hook catches and cuts the free edge of the mitral curtain, and a loud systolic murmur appears over the apex of the heart. The results of such experiments when the dogs are kept alive will be detailed in another paper. In most instances in which an extensive lesion is produced the effects offer too great a strain for the heart, and dilatation with fibrillary twitchings and cessation of the heart beat result. In one case, however, while a curve was taken from innominate vein and femoral artery a mitral insufficency was produced which proved to be so extensive that a break in compensation occurred, the arterial pressure sank to almost nothing, the heart became dilated, and with each beat there was seen a high pulsation in the innominate, due doubtless to relative insufficiency of the tricuspid. After stimulation the heart gathered strength, brought the arterial pressure back to normal, and withdrew from the distended veins the abnormal amount of blood gathered there. The excessive pulsation communicated to the veins disappeared with the contraction of the right heart to its normal dimensions. In this experiment the condition of broken compensation with recovery seemed well imitated.

Mitral stenosis was studied after its production by one of the methods mentioned above; the most satisfactory being the application of the screw clamp, which narrows the orifice without also producing insufficiency as the suture is apt to do.

When canulas are inserted into left auricle, pulmonary artery, systemic vein, and systemic artery great elevation in pressure is recorded by those in the left auricle and pulmonary artery, while within the time occupied by these experiments at least no great change appeared in the systemic veins. The arterial pressure, however, drops markedly. The diminished circulation is in the systemic vessels while the overloaded circulation with stagnation of blood is found in the pulmonary vessels (Curve 5).

In *tricuspid stenosis* on the other hand, produced in the same way, a very sharp elevation of venous pressure is at once evident, the obstructed circulation being now the systemic one (Curve 6). When *tricuspid insufficiency* was produced the effects of various lesions of the other valves, particularly of the pulmonary, upon the venous pressure became much more evident.

Every valvular lesion or experimentally produced limitation of the activity of the ventricle tends to diminish the amount of blood in actual circulation, and to allow of the stagnation of the rest in the part of the stream bed behind the incompetent portion.

In addition to the functional disturbances of the myocardium, such as were mentioned above, it was sought to imitate the effects of anatomical lesions by the actual destruction of portions of the myocardium. This could easily be done by the injection of alcohol or some similar substance into the heart muscle by means of a hypodermic syringe, the extraordinary power of the heart to maintain the blood pressure in spite of extensive injuries being demonstrated.

The experiments of Porter with the ligation of the branches of the coronary arteries were repeated, and it happened that in the experiment watched by the class, the ligature of the anterior descending branch of the left coronary vessel produced only a temporary irregularity of the heart and lowering of the pressure, while the subsequent additional ligature of the circumflex branch gradually brought the pressure and pulsation to zero.

Coincidentally with these experiments or on alternate days the anatomical study of museum preparations was carried out, the anatomical results of the experiments being compared with those of the actual disease in man. There were of course changes in the heart which could not be imitated experimentally, and the results of the prolonged existence of cardiac lesions were also for the most part impossible to attain by experiments but could be well studied in the museum.

Some time was spent in the study of congenital malformations of the heart, in which the museum is rather rich, and the effects upon the circulation of these distortions was considered.

The time did not allow of the experimental study of arteriosclerosis or of aneurysms. Such experiments, however, as well as the production of collateral tracts of circulation, etc., could be prepared beforehand, if the course were given again, but long-prepared experimental imitations of disease do not seem to present any special advantage over clinical or autopsy material, unless it be in the readiness with which they may be investigated. On that account these things were studied chiefly from their anatomical results. More immediate interest could be found in the observation of the effects upon blood pressure of the ligation or clamping of various arteries and arterial systems, it being easily shown that the ligature of both renal arteries caused a slight rise in pressure; even the aorta below the splanchnic vessels may be ligated without changing the pressure very markedly while the ligature of the splanchnics themselves causes an extraordinary rise. The effects of hæmorrhage and infusion were also studied, manometers being connected with both the general arterial and pulmonary circulation, and it is remarkable that while the systemic pressure suffers great changes, the pressure in the pulmonary circulation is but slightly altered.

The effects of various drugs, such as adrenalin, nitroglycerin, amyl-nitrite, etc., were demonstrated and it was shown that neither these nor any electric stimulation of nerves had any effect except indirectly upon the blood pressure in the pulmonary circulation (best tested by connecting a manometer with the pulmonary vein, in which the pulsation from the right ventricle is almost unchanged by the pulmonary capillaries).

Thrombosis and embolism were studied anatomically, thrombosis being especially adapted to experimental production and study while the effects of emboli in producing infarctions were demonstrated by injecting into an artery against the stream a quantity of poppy seeds. These produced extensive hæmorrhagic infarctions of the intestine and anæmic infarctions of the kidney, the white seeds being readily found where they occluded the supplying vessels.

Such in brief is an outline of the portion of this experimental course already carried out, a course experimental in two senses and definitely settled only in so far as the conviction is firm in our minds that the study and teaching by experimental methods of the pathology of function is a broad and promising field as yet by no means exhausted. Already in this new laboratory the detailed study of one or two of the conditions has been carried out with a view to the better comprehension of the resultant changes in function, and these will shortly be published. The aim of the course will be accomplished if it helps to stimulate the more minute study of the behavior of living pathological organs, in addition to the long-accustomed anatomical study of the dead organ.

PHLEGMONOUS ENTERITIS.

By W. G. MacCallum, M. D.,

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Nearly all text-books make some mention of phlegmonous enteritis, but the actual material upon which this description is based is very small. Seven cases have been described as far as can be ascertained and of these five were affections of the upper part of the small intestine while in one there was a lesion of the colon, and in another the whole digestive tract was involved. The condition is, however, so analogous to the phlegmonous gastritis that one may construct the pathological picture from that similarity. The first case reported was that of Belfrage and Hedenius[1] whose patient was a man aged 52, who was suddenly taken sick with symptoms of peritonitis. Belfrage being called in on the third day found an incarcerated hernia in the right crural region. Operation revealed an omental mass strangulated there, and the patient died.

At autopsy there was found a generalized peritonitis. At a point 40 cm. below the pylorus the jejunum became greatly widened and thickened measuring 18 cm. in circumference throughout a stretch of about 18 cm. The mucosa was grayish yellow and on the broad valvulae conniventes were seen a number of bright yellow flecks sometimes coalescing into streaks running across the intestines. Here the mucosa was occasionally ulcerated and the ulcers showed at their base a loose tissue infiltrated with pus. On incision it was found that the thickening arose chiefly from swelling of the submucosa and muscularis. The first was especially swollen and was 8 mm. thick in places, being quite loose in texture and of light yellow color. The musculature, too, was infiltrated with pus. Hedenius considered this phlegmonous infiltration to be of infectious nature and similar in that respect to the phlegmons of the subcutaneous tissue.

Goldschmidt[2] saw a similar condition in the colon of a

[1] Belfrage och Hedenius, Upsala Läkaref. Förhandl., XI, p. 132, 1876. Ref. Virchow Hirsch Jahresber. 1876, II, 210.

[2] Goldschmidt, Dtsch. Arch. f. klin. Med., 1886-7, Bd. 40, p. 400.

woman aged 41, who after an indiscretion in diet had a chill, pain in abdomen, cough and pain in her chest. Obstipation and meteorism were continuous with severe pain in the abdomen until her death on the tenth day.

At the autopsy the peritoneum over the transverse colon and small intestine was dulled by fibrin and by an exudate of thick yellow pus. The transverse colon was widened to a circumference of 30 cm. the mucosa covered with thick mucus. It appeared mottled with pale and bloody suffused areas and on section was found to be extensively infiltrated with pus. In places the serosa alone persisted, the remainder of the wall being ulcerated away and this in one place was perforated.

Goldschmidt explains the condition as being analogous to gastritis phlegmonosa, the infection occurring primarily in the mucosa and extending later to the submucosa. Atony of the intestinal musculature allows of coprostasis which is soon followed by ulceration of the mucosa and extended infection. It is questionable whether there is any relation between this infection and the pneumonia which was also found.

Hofman[3] reports a case of phlegmonous enteritis in a Russian journal. The anatomical diagnosis reads as follows: Hypertrophia ventriculi sinistr. cordis. Atrophia fusca musculi cordis, dilatatio et sclerosis aortæ, Pleuritis adhæsiva chr. duplex partialis, emphysema et œdema pulmonum. Peritonitis acuta purulenta; hyperplasia acuta lienis. Degeneratio parenchymatosa hepatis. Gastritis chronica polyposa. Tumor (adeno carcinoma) curvaturæ minoris ventriculi cum exulceratione. Enteritis phlegmonosa circumscripta intestini jejuni. Enteritis acuta hæmorrhagica intestini ilei. Colitis chronica. Nephritis interstitialis chronica et acuta parenchymatosa.

The remainder of the paper being in Russian, I cannot read it.

Askanazy[4] reports a similar case. It was that of a man aged 51, who fell into a hole and injured his knee. This disabled him for several days, during which time he suffered from severe pain in the abdomen. After making an indiscreet attempt to walk, he became worse and died sixteen days after the injury. At autopsy 50 cc. of thing purulent fluid was found in the peritoneum. The intestinal folds and especially the duodenum and jejunum were greatly enlarged, the jejenum measuring 12½ cm. in circumference. The mucosa beginning at a sharp line was greatly swollen, rather transparent and gray, the valvulae conniventes being 1 cm. high. The crests of the folds were in places brown and necrotic with small defects through which the infiltrated yellowish tissue below appeared. At many points pus welled out. Section showed a purulent infiltration of the entire wall, the submucosa being converted into a broad layer of purulent tissue. The affected part of the jejunum was 20 cm. long. Cultures showed the streptococcus and staplylococcus albus, which were also found in sections.

Microscopically the infiltration is chiefly in the submucosa and muscularis, the mucosa itself being relatively unaffected. Askanazy thinks that trauma is important in producing this and that as the jejunum is fixed, it is most of all likely to suffer rupture in such a fall as this patient had. To support this he refers to several cases of traumatic rupture of the jejunum. Further he regards the streptococcus infection as coming directly from the intestine.

P. Matthes[5] describes a case observed in Dresden in which the whole intestinal tract including the stomach and colon was affected. The case was that of a woman aged 53 years who had suffered no traumatism, but in whom the abdomen gradually became distended. Great œdema of the legs ensued but throughout the temperature was normal. Three days before death erysipelas appeared in right leg.

At the autopsy there was found a widespread fibrinous peritonitis. The liver was in a state of advanced cirrhosis, the spleen greatly swollen, the intestine throughout thickened and rigid, the thickening of the wall being due especially to purulent infiltration of the submucosa, which was most marked in the jejunum, about the cæcum and in the stomach. Streptococci were found in smears, and in cultures from the walls. The author attempts to explain the mode of infection by the possibility that the ascites produces slight injuries of the mucosa of the jejunum, which is tightly bound down, which allow of the entrance of organisms from the intestine. More probable, however, in his opinion, is the injury and infection of the intestine by the needle used to evacuate the ascitic fluid. A third possibility is the metastatic infection from the erysipelatous patch.

Deutelmoser[6] describes the case of a farmer aged twenty-one years, who was well up to 14 days before his entrance into the hospital. At that time he took to his bed with vomiting, pain in the abdomen and jaundice. On admission the abdomen was distended, tender in epigastrium and mesogastrium where there was a definite resistance which could be outlined. Vomiting frequent, but the vomitus was not blood stained, and gave an acid reaction. Icterus was quite deep. Several days later the abdominal tumor was still readily palpable and gastric succussion was to be heard over it. Vomiting frequent. Temperature normal or subnormal. Death occurred 25 days after admission to hospital with sudden elevation of temperature.

Autopsy: Most of the intestine appeared normal, the duodenum much thickened, the region of the bile papilla being especially affected, and causing great dilatation of the bile ducts. The wall of the intestine was 10 mm. thick, the mucosa intensely yellow and œdematous. There was no peritonitis. Deutelmoser inclines to the idea that this infection was due to some slight lesion of the mucosa of the duodenum, which allowed of the invasion of the streptococci from the intestine.

[3] Hofman, Bolnitschnaja Gazeta Botkina, 1896.

[4] Askanazy, Centralbl. f. Allg. Pathologie, Bd. 6.

[5] P. Matthes. Ein seltener fall von phlegmonöser Darmentzündung. Inaug. Diss. Leipzig, 1905.

[6] Deutelmoser, Ueber enteritis phlegmonosa idiopathica. Inaug., Diss. Greifswald, 1905.

In addition to the cases already cited, he quotes another Russian paper by Moissejew,[1] who described the case of a peasant aged 67 years, who died after a brief illness characterized by pain in the abdomen but no fever. There was peritonitis and swelling of the jejunum throughout 40 cm. The mucosa was grayish yellow, opaque and swollen. The folds of the mucosa broad and flat; no visible injuries were present. The submucosa was in places 5 mm. thick, grayish white and exuded a milky fluid. These changes reached their maximum 20 cm. from the end of the duodenum, after which they faded gradually away. The rest of the ileum and the colon were unaltered. Microscopically and culturally the streptococcus pyogenes was found.

The case which we have observed was as follows:

John Chase, aged 75, a negro laborer was brought into the hospital complaining of pain in the abdomen and vomiting. He himself was unable to answer questions as to his past history, but it was ascertained that about three weeks before he had been struck by a street car, and carried unconscious to the Maryland General Hospital. The only injury seemed to be a scalp wound, but during the week that he remained in the hospital he complained of considerable pain in the "stomach." After coming home he seemed to be quite well up to the beginning of the present illness.

Present illness: 4 p. m., November 4, 1905. Patient awoke at 5 a. m. yesterday (November 3) with pain in the abdomen, which, however, he is unable to locate very definitely. In a general way he places his hand over the lower right ribs, and across the epigastrium and left flank as the site of the pain. Pain was apparently quite severe, although no definite history of cramps can be obtained. Shortly after the onset of pain the patient began to vomit and has vomited at short intervals ever since. At present he regurgitates every few minutes, without effort, a mouthful of yellowish bile-stained fluid of a foul, faintly fæcal odor. Patient states that bowels moved very slightly yesterday morning.

Note by Dr. Sowers:

Patient looks ill, tongue moist, lips dry, no very marked expression of pain. Abdomen. Symmetrical, rather full, but not distended. There is slight bulging in each flank, but it is everywhere soft. There is some general tenderness on deep palpation, but no muscle spasm. Apparently the tenderness is slightly greater below the umbilicus. There is relative dullness in the left flank. Liver dullness extends to costal margin, but neither liver nor spleen can be felt. On pressure in the epigastrium a great deal of gurgling and succussion can be made out, although there is no marked distension in this region. There is suggestive peristalsis visible over the abdomen, but no definite cramps; soreness is sufficient to make the patient lie on his side. Temperature 100°F. Leucocytes 24000, urine contains albumen and numerous granular casts.

Operation. Because of the signs of high obstruction exploratory laparotomy was decided upon, although the patient's condition was very bad.

No general peritonitis was found, but in the left side of the abdomen there was found a slight excess of turbid fluid. Cæcum and appendix, pelvis, gall bladder and liver, and stomach were explored and found normal. Nothing abnormal was found in the large intestine nor in the small intestine up to a point about 25 cm. below the duodenum. At the beginning of the jejunum, just beyond the point where the duodenum crosses the spinal column, the bowel wall was very markedly thickened, and had a brawny appearance. This distended loop was situated low down beneath the spleen, below the splenic flexure of the colon, and when it was drawn out a small amount of turbid fluid was found about it in this corner of the abdominal cavity. This was wiped out. The distended loop seemed not to have been kinked, and at no point was there an evident obstruction. The color of the bowel was a little darker than that of the surrounding bowel, but there was no evidence of any local pressure or strangulation, and the circulation in the mesentery seemed normal. The increased size of the bowel, which was perhaps 5 cm. in diameter, whereas the bowel below this loop was only about 2½ cm. seemed to be due to the thickening of the walls rather than to the distension of the loop. On palpation the much enlarged rugæ could be felt. There was no sign of ulceration or perforation. The serous coat was, however, slightly injected and there were a few fine flakes of fibrin upon its surface, which had lost in part its gloss.

Nothing further was found to account for the condition, although there was felt a hard mass in the region of the left kidney, which was thought to be either a calcified retroperitoneal gland or a renal calculus.

The patient's condition did not permit of any further operative interference even had there been any clear indication for such procedure, and he gradually grew weaker and died about 1 a. m. November 5th.

Autopsy was performed a few hours later. From the protocol those portions are copied which are of interest in this connection.

The body is that of a small man 165 cm. in length. There is a wound about 20 cm. in length in the median line closed with silver sutures. A smaller wound in the left flank has been made to receive a protective gauze drain. In the peritoneum there is a little blood-stained fluid, but the purulent fluid found at the operation is no longer present. The omentum, duodenum and adjacent tissues are somewhat reddened, but there is no distinct fibrinous exudate on their surface. The appearance is practically what might be expected after handling the abdominal organs. The greater part of the intestine is collapsed and lies in the pelvis. The appendix is quite free and normal looking. Mesenteric glands are not especially enlarged, except one that lies opposite a high point of the intestine. This one is not caseous but opaque and indurated and on section swollen-looking. The thoracic viscera show no abnormality.

[1] A. J. Moissejew, Bolnitschnaja Gazeta, 1900, No. 33.

Spleen and liver are practically normal, the gall-bladder containing clear green bile, which passes easily through the ducts, although there is in the duodenum a small concretion resembling a gallstone. The gall duct and bile papilla appear entirely normal.

The stomach is not dilated. It contains a greenish fluid. The mucosa is everywhere thickened and studded with prominent mushroom-like polypoid masses, about thirty in number. The largest of these is no more than 1 or 2 cm. in height and 1.5 cm. in diameter. The mucosa is covered with thick mucus, and shows abundant ecchymoses. Just below the pyloric ring there are one or two small, irregular, punched-out ulcers in the mucosa. The intestine viewed from the outside is greatly enlarged from a point about 5 cm. below the pylorus for a distance of about 30 to 35 cm. It is not only distended but its walls are greatly thickened so that it stands out as a stout rigid tube, which gives place abruptly, lower down, to the normal collapsed intestine. The abrupt transition between the thickened and the normal part can be plainly felt by the palpating finger, as was observed at the operation. No kink is found at this point nor any narrowing to explain the symptoms of obstruction. The serosa covering the rigid portion is somewhat dulled but there is no conspicuous deposit of fibrin upon it.

On cutting open the intestine its lumen is found to be perfectly open and filled with a soft, yellowish white, pasty, granular material. On removing this the mucosa is seen to be remarkably altered. It is very pale, grayish white in color, and there are no visible ulcerations or defects in its surface, a few minute hemorrhages only being seen. The lining of the intestine differs from the normal, however, in that the transverse plicæ instead of being thin, soft flaps of mucosa stand up as thick, opaque, swollen, and rigid folds, sometimes reaching a height of 1 cm. or more and returning to their erect position when bent over. This change is most intense at a point about 15 cm. from the pylorus, but it extends throughout a length of about 30 cm., that is from a point about 5 cm. below the pylorus to a point 35 cm. below, where the folds again suddenly resume the normal aspect.

On making an incision across one of these swollen, firm, valvulæ conniventes it is seen that the swelling is not in the mucosa itself, which appears on the cut edge as a thin, opaque, grayish white line forming the surface. The submucosa, however, is very greatly thickened and is gray and translucent and moist. On squeezing it a slightly turbid fluid oozes out, and the tissue collapses into a soft spongy mass. No such infiltration can be definitely seen macroscopically in the musculature.

The mesentery of this part of intestine is not thickened or grossly altered in any way. The blood vessels are perfectly patent and contain fluid blood. The left kidney is much contracted about some calcified masses of mortar-like material; its ureter is obliterated.

The other organs show nothing of special interest.

Numerous cultures were made from the tissues in this case, but through some misfortune they were lost and the organism concerned can only be described morphologically.

Sections of the intestine in the affected area show a remarkable condition. The mucosa is everywhere practically normal. It is true there is a considerable desquamation of epithelial cells, but those which line the crypts and in large part those which cover the villi are intact. The stroma of the mucosa shows practically only its normal cells, there being little if any infiltration with leucocytes. The muscularis mucosæ, however, is spread apart and immediately upon passing through it into the submucosa the most extensive infiltration is met with. The tissue elements of the submucosa are widely separated and isolated by an accumulation of fluid and cells with a delicate network of fibrin, which extends everywhere among them. The cells are so abundant as to form a homogeneous mass which occupies the whole area of the section of the fold and everywhere separates the mucosa widely from the underlying musculature.

Not only is the submucosa so infiltrated, but the musculature shows the same condition, the muscle fibers are spread apart and isolated in bundles of various sizes, by quantities of cells with fluid and fibrin. Even the subserous tissue is densely infiltrated, and along the edge of the section its surface is seen to be covered with a thin layer of fibrin. The cells are chiefly of the polymorphonuclear neutrophile type, but there are mononuclear cells scattered among them in limited numbers. These are larger than the more abundant leucocytes, and possess a large vesicular nucleus. They vary a good deal in size, however, some being smaller and resembling the lymphocyte more closely while others are very large and are evidently very actively phagocytic since they often contain the bodies of other cells. The lymphatic channels are sometimes seen stuffed with these various types of cells, and the same cells are recognized on closer examination of the infiltrated muscularis. Section of the adjacent mesentery also shows an acute inflammatory infiltration, the lymphatic channels there also being filled with cells. Weigert's fibrin stain brings out very clearly the delicate network of fibrin which stretches among the cells and also demonstrates the presence of myriads of bacteria, most of which are enclosed in the polymorphonuclears, although a certain number are free. These are micrococci in chains, and there seems little doubt that the organism is the *streptococcus pyogenes*. The cocci are rather elongated however at time and occur in pairs, but in general they form short chains, which may be entirely engulfed by the leucocytes.

It is interesting to note that the neutrophile leucocytes exhibit an extraordinary avidity for these organisms, while they seem but little attracted by fragments of other cells. On the other hand the mononuclear polyblastic elements apparently do not ingest bacteria, but do eagerly engulf other cells and fragments of cells, and only when these had contained cocci are the organism to be found within the body of the large cell. Evidently the two types of cells respond almost specifically

to certain chemiotactic stimuli, a fact which is of course well enough known.

There is, therefore, a close resemblance betwen this case and the others which have been described. Askanazy's case is especially similar not only in that there was a history of traumatism, but also in its clinical and anatomical features. It seems plausible, as Askanazy suggests, that traumatism to the abdomen may affect the upper part of the intestine most readily on account of its relatively fixed position and thus give rise to a chance for infection. It is of course possible that the bacteria invade directly from the intestine, but in the light of the recent work upon the relative freedom from bacteria of the uppermost part of intestine, it seems also possible that the trauma may have produced a point of lowered resistance into which streptococci are carried by the blood from elsewhere. The mucosa in this instance was so completely intact over the affected area that some support is lent to this latter view.

Little else can be said in general about a condition which has been so rarely observed. Diagnosis must remain very difficult unless aided by an exploratory laparotomy, but the symptoms of obstruction which in this case were doubtless due to the paralysis of peristalsis throughout the affected part of the intestine, together with the pain and high leucocytosis may perhaps offer some suggestion as to the nature of the condition. On exploring the abdomen the rigidity of the bowel once seen could hardly be mistaken for anything else, especially when a definite obstruction cannot be found and when there is also evidence of peritonitis.

Suggestions as to treatment are not backed by experience of good results since all reported cases have quickly died, but enterostomy below the paralyzed area might at least relieve the symptoms of obstruction. With such an extensive focus of infection within the abdomen and involving generally the duodenum and jejunum, the outlook seems very grave under the best of circumstances.

MULTIPLE CAVERNOUS HÆMANGIOMATA OF THE INTESTINE.

By W. G. MacCallum, M. D.

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A case has recently come under observation in this laboratory which shows throughout the small intestine many small cavernous venous tumors, a condition which seems to have been observed by few, if any, other writers. There is so little in the literature bearing upon the subject that it is possible for me to give in abstract all that has been found after fairly careful search.

Laboulbéne[1] described an erectile tumor of the intestine, which gave rise to a fatal hæmorrhage. The case was that of a man aged 64, who had suffered from slight constipation which was however easily relieved by mild purgatives. One morning he passed blood in the stools. This lasted for several days after which the stools were normal. One month later this was repeated and he vomited black coagulated blood, but after two or three days his condition seemed normal. Physical examination was negative and the physician regarded the case as one of ulcer of the duodenum. A few days later there was an extensive hæmorrhage from the bowel and the patient died. At autopsy the intestine was found full of blood; in the duodenum above the bile papilla there was a tumor of about the size of an almond, elevated and covered by mucosa except for a ragged ulceration which lay bare the tumor tissue. This was composed of widened capillaries dilated regularly or laterally into saccular dilatations.

Laboulbéne considered the tumor to be an angioma developing in the mucosa and emphasized the danger of hæmorrhage in such cases.

Boyer[2] describes a case in a man aet. 62, who on dying of pneumonia, showed at autopsy numerous small varices in the jejunum and the upper part of the ileum. There were rounded blackish nodules visible by transmitted light, the largest being of the size of a pea, while most of them were much smaller. They were very closely set throughout the tissue. No alteration of the larger arteries or veins could be found, but when examined with a lens, these nodules appeared to be situated upon arterial loops and to be themselves formed of vascular loops like a renal glomerulus. They were fairly sharply outlined and the walls of the vessels which were twisted together to form them were parallel and in continuity with those of the arterioles. There were no aneurysmal dilatations or ruptures, and a connective tissue envelope surrounded them at least in part so that they could hardly be entirely emptied of blood.

Paci[3] reported the case of a woman who, having suffered for a short time from obstruction of the intestine, suddenly passed together with fæces, a mass of tissue which Paci recognized as a pedunculated cavernous tumor. The central portion was composed of a cavernous tissue with large lacunæ filled with clotted blood. Capillaries were numerous in the trabeculæ and the whole was covered with mucosa. Apparently hæmorrhage had occurred into the substance of this tumor, enlarging it to such an extent as to cause obstruction after which it was torn from its peduncle and passed out, the obstruction being thus relieved at once.

Hektoen[4] describes in a case of aortic and mitral endocarditis, many large veins running transversely under the mucosa like varicose veins, occasionally anastomosing and sometimes overlapping. These occupied a limited area of the

[1] Laboulbéne, Bull. de l'Acad. de Méd., 2 ser., t. I., 1872.

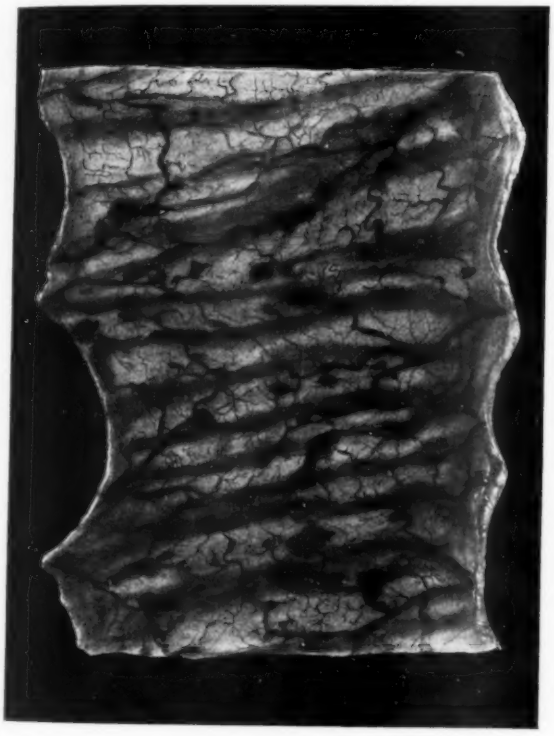
[2] Boyer, Bull. de la Soc. Anatomique de Paris, t. 52, 1877.

[3] Paci, Lo Sperimentale, 1882, p. 149.

[4] Hektoen, Trans. Chicago Path. Soc., 1897-9. 1900, iii., p. 192.

small intestine and sometimes presented globular dilatations full of blood. Microscopically they proved to be irregularly dilated venules, and Hektoen speaks of the condition as a simple hæmangioma.

Our case differs from all of these in certain respects. It was as follows: C. Y., white male aged 54 years, a salesman who had had no infectious diseases except pneumonia, complained only of digestive disturbances which had lasted for months. He vomited before breakfast and once two years ago vomited a quantity of blood. In the present illness he has had headache and dizziness and frequent micturition. Had always been an excessive whiskey drinker, and on entering the hospital had drunken to great excess and was in a condition of acute alcoholism. Death occurred April 10,



1905, and the autopsy was performed a few hours later (No. 3513).

Anatomical diagnosis.—Arteriosclerosis; atrophy of cerebral convolutions. Chronic diffuse pancreatitis; beginning cirrhosis of liver; œdema of brain. Broncho-pneumonia; multiple cavernous angiomata of intestine.

There was nothing in the other lesions which seemed to bear directly upon the appearance of the angiomata, so that they will not be described in detail. The small intestine seemed practically normal throughout as far as the mucosa was concerned, but throughout its length and especially in the upper portions there could be felt either from the inside or from the peritoneal side small fairly firm areas which shone through the mucosa as blackish purple patches, the largest of which reached a diameter of not more than 7 or 8 mm. By transmitted light these were plainly seen as dark red thick nodules situated in the course of the veins and connected by abundant branches with the larger veins.

They were thought at first to be hæmorrhages since they seemed in many cases to be clotted drops of blood under the mucosa. On cutting through them, however, it was found possible to squeeze out liquid blood which left a spongy tissue mass. Sometimes the clots were visible, adhering in this spongy tissue.

The mucosa was in no way altered over these nodules, and there appeared to have been no hæmorrhages from them at any time. They were quite numerous, perhaps forty, to be found throughout the whole affected portion of the ileum, a portion of which is shown by transmitted light in the drawing which was kindly made for me by Mr. Shore. It can be seen that they are irregular in outline and in density as if composed of a plicated mass of vessels. Sections show that these nodules are in reality not hæmorrhages but vascular tumors of cavernous structure composed of wide sinus-like spaces lined by endothelium and full of blood. They lie chiefly in the submucosa, not invading the mucosa itself nor extending to any degree into the musculature, although in places portions of these dilated channels may be found among the muscle bundles.

On approaching such a nodule it is found that the veins of the submucosa in the neighborhood are very numerous, large, and tortuous and at the margins of the nodule suddenly become widened and pass over into widely anastomosing blood channels, the walls of which consist of little more than the endothelium and one or two layers of fibrous tissue. The arteries are easily distinguished wherever they occur, from these sinuses which rapidly coalesce as one approaches the centre of the nodule and form large, irregular sacs. Some of these are partly thrombosed and contain masses of leucocytes, the thrombi sometimes showing a definite architecture, sometimes being granular or hyaline. Toward the center of the nodule the mucosa is separated very widely from the musculature by the tangled mass of blood sinuses, which open so widely into one another, that the cavernous character becomes very evident even from a single section, in which the partitions between the large blood spaces are seen to end abruptly in the centre of a space. No hæmorrhage seems to have taken place from these angiomata, although it is possible that the vomiting of blood which occurred two years before the man's death may have been due to the rupture of one of them.

Since this paper was finished there has appeared a short paper by H. Bennecke in the last number of Virchow's Archiv, Bd. 184, Heft 1 "Ueber kavernöse Phlebektasien des Verdaungstraktus," in which the author describes a case practically identical with the one described here except in that the cavernous "phlebectasies" existed throughout the œsophagus and stomach, as well as the intestine, and concludes that they resemble in their general nature the cavernous angiomata of the liver.

ON THE MECHANICAL EFFECTS OF EXPERIMENTAL MITRAL STENOSIS AND INSUFFICIENCY.

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AND
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The pressure relations in mitral stenosis are quite simple and easily understood, even when, as is so often the case, it is complicated by the existence of mitral insufficiency. It differs from a pure mitral insufficiency essentially in that the right ventricle and left auricle are unable to force the blood into the left ventricle which assumes no part of the responsibility, while in mitral insufficiency the stagnation of blood in the lesser circulation may be, in some degree, at least, favorably influenced by the increased activity of the left ventricle. In the one case the obstruction is obviously at the valvular ring; in the other it consists in the ineffectual mechanism of the left ventricle, part of the work of which is wasted.

Curves illustrating the change in pressure in the various parts of the circulation in experimental mitral stenosis may be introduced to illustrate the condition. Experimental stenosis is readily produced by one of several methods, either by applying a screw clamp with arms guarded by rubber tubes, or by passing a suture about the auriculo-ventricular ring or by introducing a distensible balloon through the auricular appendage. The immediate result is the lowering of the general arterial pressure and the great elevation of the pressure in the pulmonary arteries and in the pulmonary veins and left auricle. The pressure in the systemic veins is little if at all elevated, unless there arise an insufficiency of the right ventricle or, with the dilatation of the right ventricle, relative insufficiency of the tricuspid valve. The essential feature of the process, as indeed of all the changes of blood pressure due to any obstruction of the blood stream from alterations of the heart, lies in the fact that the amount of blood in actual circulation is diminished while the rest of the blood stagnates behind the obstruction, and therefore in this case in the pulmonary circulation. (Curve 1.)

In mitral insufficiency we find again precisely the same principle: the incompetency of the mitral valve to maintain the direction of the stream for all the blood, renders a part of the work of the left ventricle useless, and the result is that the general arterial and systemic pressure falls while that in the pulmonary veins tends to rise. In other words the quantity of blood kept in circulation is decreased, the remainder stagnating behind the incompetent valve.

Insufficiency of the mitral valve may be easily produced experimentally by means of a hook with blunt point and inner cutting edge such as is shown in Figure 1. This we had made in such a way that the outer surface is very smooth and round so that only thin structures such as the chordæ tendineæ and valves are reached by the knife edge. This hook is introduced through the left auricular appendage into the left ventricle where the valves and chordæ tendineæ may be cut to the desired extent. Canulas connected with mercury manometers having been adjusted in various parts of the circulatory system, the one designed to record the pressure in the left auricle, is quickly tied into the aperture in the auricular appendix on the removal of the hook.

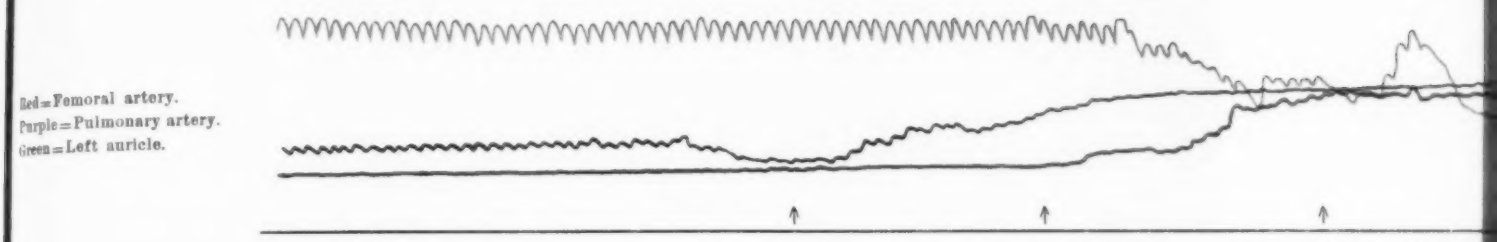
It is now found by comparing the curve with that recorded before the insufficiency was produced, that great alterations have immediately taken place. The arterial pressure always sinks; the degree of lowering depending upon the extent of the insufficiency. Its pulsation is not greatly altered. The pressure in the pulmonary artery is relatively little altered; with extreme insufficiency it usually sinks with the general arterial pressure; with slight insufficiency it rises but not very high.

The systemic venous pressure is also not greatly altered. The most striking change is seen in the curve from the left auricle in which before the injury to the valve there is low pressure and only the slightest waving pulse. Now the blood is ejected from the left ventricle not only into the aorta, but also directly into the auricle and with extreme insufficiency, the auricle may be regarded as forming part of one chamber with the left ventricle. It is therefore not surprising that it is seen to become distended with blood and to beat violently and synchronously with the ventricle. The manometer connected with it shows that the pressure becomes markedly elevated and the curve shows great excursions which are due to the contractions of the left ventricle. This was clearly described by von Basch[1] from his experiments with his model and he states that the results of animal experiments are the same.

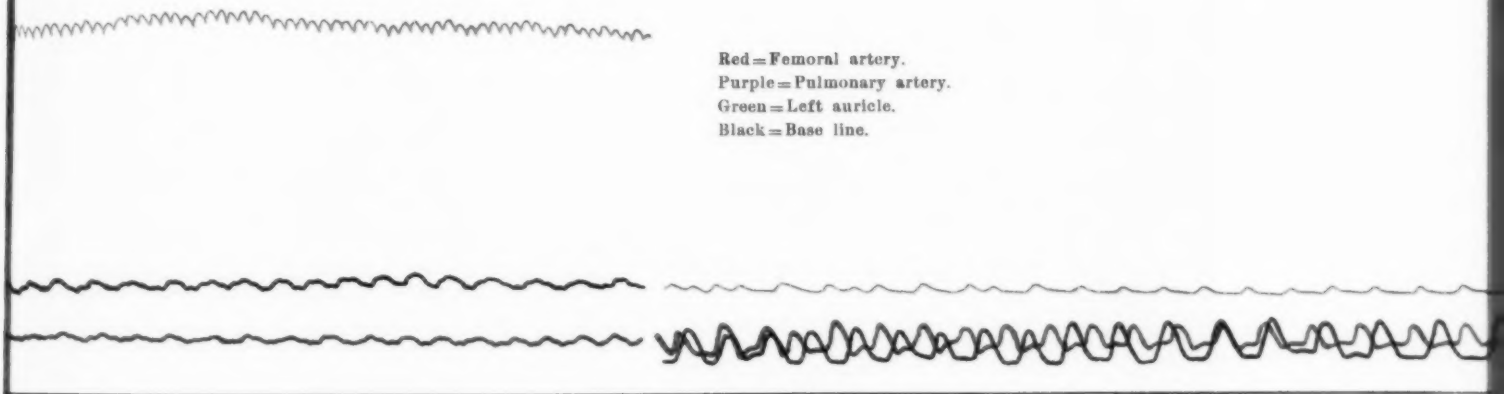
In all these experiments the heart was carefully examined at autopsy, and it was found that in each instance the hook had cut some of the chordæ tendineæ and had made a more or less extensive rent in one or both curtains of the valve.

It is evident that the disturbance produced consists in placing the left ventricle at a disadvantage in that an orifice is made in its wall so that in its contraction the blood escapes not only in the normal direction, but backward also. Unless therefore it pumps more actively and controls a larger amount

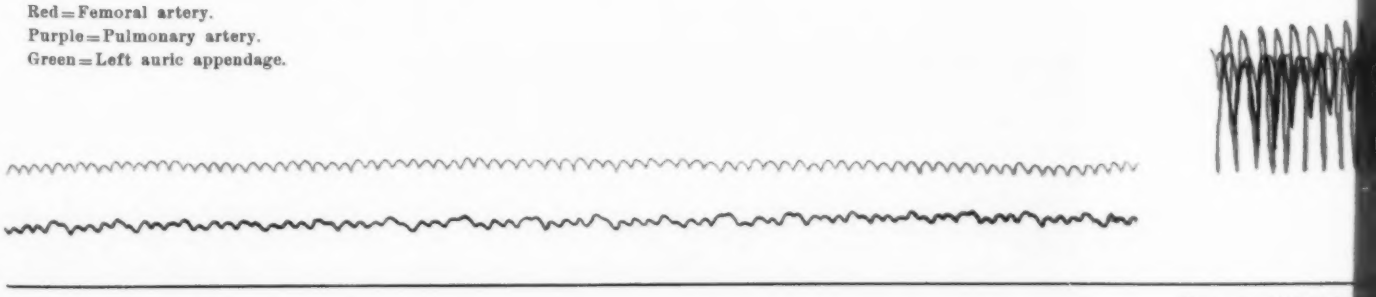
[1] v. Basch, Allg. Physiologie und Pathologie des Kreislaufs. Wien, 1892.



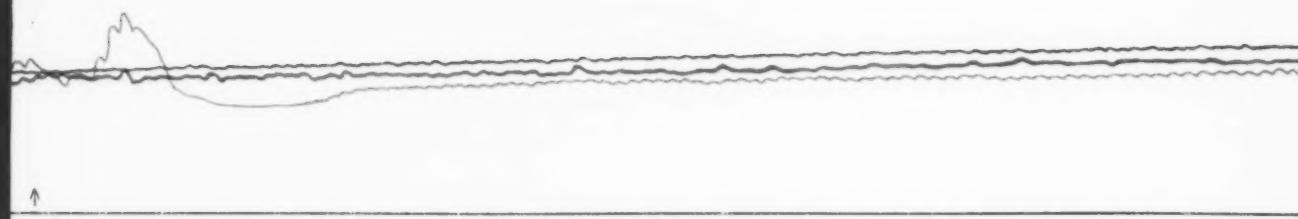
Curve 1. Mitral St



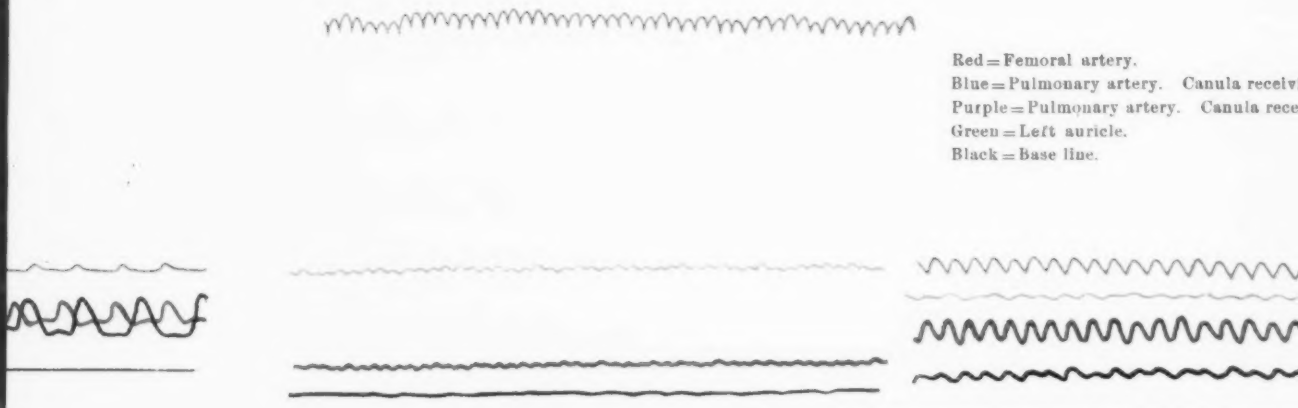
Curve 2. Mitral Insufficiency



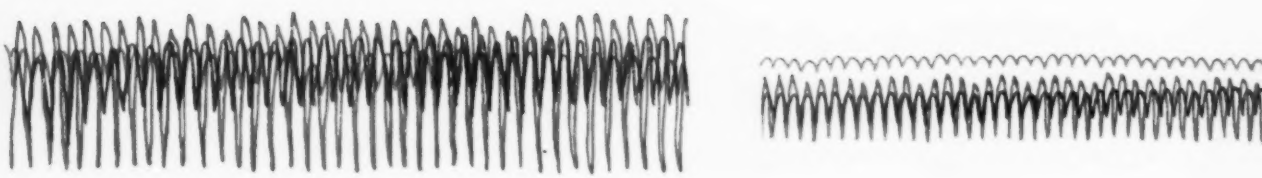
Curve 3. Mitral In



Curve 1. Mitral Stenosis.

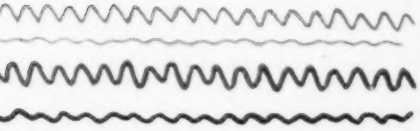

Red = Femoral artery.
Blue = Pulmonary artery. Canula receiv
Purple = Pulmonary artery. Canula rece
Green = Left auricle.
Black = Base line.

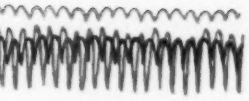
Curve 4. Mitral Insufficiency.



Curve 3. Mitral Insufficiency.

ula receiving pressure from right heart.
anula receiving pressure from lung.





of blood, the amount ejected into the aorta will be diminished. Whether in the case of mitral regurgitation the amount thrown into the aorta can ever reach the normal is one of the questions which first presents itself. It is of course obvious that in order that the circulation may continue, precisely the same amount must be thrown out by the right and left ventricles, for one ventricle could not eject more than the other for any length of time without finally forcing the greater part of the blood into the vessels which lie in front of it. Further it seems clear that although the amount of blood handled by the heart in one beat is a very small portion of the whole mass of the blood, and although the position of the greater part of the blood may be changed by vascular contraction and dilatation, all of the blood is moving at all times and under ordinary conditions its actual amount does not change. Hence one may reason that if for any cause the left ventricle fails to perform its normal work and throws out a smaller quantity of blood the amount furnished to the right auricle and ventricle will also decrease. By active contraction of the vessels the normal amount might be kept up for a few heart beats, but this reserve would soon be exhausted and the systemic organs left anæmic while the blood is crowded into the pulmonary circulation. This has been pointed out by Kornfeld, who finds that the venous pressure falls with a fall in the arterial pressure.

From this it is seen that when regurgitation occurs at the mitral valve the amount of blood thrown into the aorta must be constantly less than normal as long as the cavity of the ventricle retains its normal dimensions and the wall its normal force of contraction. This may be modified by the power which the ventricle possesses of dilating to receive more blood and expelling it with great force; but in order to throw the normal quantity of blood into the aorta the left ventricle must receive that amount plus the amount regurgitated. This is possible, however, in only one of two ways, either there must be an actual addition of fluid to the blood from somewhere to make up to normal the smaller amount thrown into the aorta, or there must be such a vascular contraction that when the diminished amount thrown out by the left ventricle reaches the venous side of the heart the amount is made up to normal by the narrowing of the vessels, and thus while the circulating amount is maintained at the normal, the actual amount in the tissues and larger vessels is diminished by so much as has accumulated in the lungs. Probably there would in such a case be a rapid addition of fluid to the blood from the ingested fluid, and the total amount of blood would be increased by as much as accumulates in the lungs. Indeed one receives the impression from observing the amount of blood in the vessels at autopsy in cases of long standing chronic passive congestion from cardiac lesions, that there is a great increase in its quantity.

In our experiments we have not attempted to measure the quantity of blood thrown out by a beat of the heart, but merely the pressure which is of course very different and since it also depends upon the resistance and degree of contraction of the vessels gives only a rough clue as to the quantity of blood concerned.

The changes in the distribution of the blood may be thought of perhaps in terms of numbers quite arbitrarily selected to represent the amounts of blood concerned. This is of course entirely schematic but it serves as a concise way of describing the probable changes. Thus if the amount handled by any one part of the heart in one systole, say the right ventricle, be represented by 10, the left auricle will receive 10 and the left ventricle also 10. If now insufficiency of the mitral valve arises a portion, say 4, is driven back from the left ventricle into the left auricle and 6 goes on into the aorta. With the same systole 10 again reaches the left auricle and meets the 4 regurgitated from the ventricle so that the left auricle now contains 14. That which follows will depend upon the activity of the left ventricle. If it will not receive more than the usual 10, 4 remains stagnant in the auricle, 6 is thrown into the aorta and 4 more regurgitates. By this time 6 is thrown into the auricle from the right ventricle instead of 10 and meets with 8 of regurgitated blood making up 14 of which 10 again goes into the ventricle. Thus the circulating blood amounts to 6 while the stagnant blood in the pulmonary circulation amounts to 4. The right ventricle forces 6 into a pulmonary circulation already containing 4 and into which the left ventricle simultaneously forces 4.

It is usual, however, for the left ventricle under such circumstances to dilate and to exert greater force in the expulsion of the greater amount of blood received, we may imagine then that the left ventricle dilates to receive the whole 14 of blood from the auricle. Even so it is probable that the amount regurgitated would now be greater than 4, and that thrown into the aorta less than 10, but if we suppose the ventricle to regurgitate 4 and throw 10 into the aorta, we now find only 6 furnished by the right ventricle to meet the 4 regurgitated, while 10 is by this beat sent on into the veins. This is the point mentioned above at which there must be, in order that the normal amount be maintained in circulation, either an actual addition to the amount of blood in the body or the veins must contract so that instead of giving up only the 6 sent to them by the aorta they are drained of 10, with the next beat they receive only the normal 10 and not the extra 4 which was removed and in order that they may return to their normal degree of contraction there must be more fluid brought to them from the tissue. All this seems possible and indeed even greater quantities of blood may be handled by the heart, and probably must be, if the normal amount in circulation is to be maintained.

A more probable state of affairs may be represented as follows: when the left ventricle has thrown 6 into the aorta and there is 14 in the auricle the ventricle dilates at the next diastole, not to receive the whole 14, but sufficiently to receive 12. Of this it expels 8 into the aorta while 4 is again regurgitated. The regurgitated 4 meets now with 6 driven in by the right ventricle and 2 left behind from the 14, making in all 12. With the next diastole the ventricle

receives the whole 12, regurgitates 4, and throws 8 into the aorta. By this time the amount 8 thrown out by the ventricle into the aorta reaches the auricle and meets the 4 regurgitated. The whole 12 passes into the ventricle and thus a circulation is established in which 8 circulates while 4 is regurgitated with each systole.

Still another case may be mentioned. The left auricle receives 10 and regurgitates 6, throwing 4 into the aorta. At the second diastole 16 being in the auricle, the ventricle dilates to accommodate the excess of blood, but can receive only 12, 4 remains stagnant. Of the 12, 6 is regurgitated and 6 thrown into the aorta. Four remaining in the auricle plus 6 regurgitated plus 4 received from the right ventricle makes up 14. Of this the ventricle receives again 12, leaving 2 regurgitating 6 and expelling 6. The condition established is a circulation of 6, with a regurgitating of 6 and a constant residue in the pulmonary circulation of 2. This probably represents a common condition in which as in the first example there is some blood constantly stagnant in the pulmonary circulation while with each systole more is introduced.

Let it be repeated that it is of course not intended to convey the idea that these figures really represent the condition or the changes in them the actual character of the changes in distribution of the blood. They may only stand as symbols to illustrate the general principles involved and are far too rough when we consider the various ways in which the different parts of the circulatory system adapt themselves to the conditions forced upon them. It is especially evident that no allowance is made for the different proportions of regurgitated and ejected blood which would arise with changes in the quantity received by the ventricle and the force exerted.

From this discussion it is, however, clear that unless the ventricle is capable of receiving and handling all the blood which fills the auricle at each systole there will be some constant obstruction to the outflow of blood from the auricle, and this is important, since Gerhardt in a recent paper (Verhandl. des Kongresses für innere Medicin, 1905), states that in the diastole of the ventricle there is no obstruction to the emptying of the overfilled auricle—that the obstruction really occupies only the portion of systole during which blood is being driven back into the auricle.

In each of our experiments there has finally arisen a dilatation of the heart, especially marked in the left ventricle, with diminished vigor and lowering of the pressure in all the curves. This may be expressed as follows: Take for example the condition in which 8 is circulating, while 4 is regurgitated at each systole. The left ventricle receives 12; with the weakening of its beat, it regurgitates 4 but drives only 6 into the aorta; at the next beat since the ventricle retains 2, it receives 12 and is distended to hold 14, again it drives out 6 into the aorta and 4 into the auricle. By this time 6 only reaches the auricle from the right heart and the left ventricle which retained 4 from the last systole receives 10 from the auricle, thus maintaining a circulation in which only 6 is circulated, 4 is regurgitated and the left ventricle is constantly receiving 14. Or the left ventricle may regurgitate only 2 and drive out into the aorta only 6. There is a residual amount of 4 to which is added in the next diastole the 2 regurgitated and the 8 previously forming the amount circulated. Of the 14, 2 is again regurgitated and 6 thrown out into the aorta. The diastole brings to the ventricle only 6 from the systemic circulation and the regurgitated 2 which with the residual 6 restores the 14 in the ventricle. The circulating blood is now only 6, the regurgitating only 2. It is easy to see that under such circumstances the pressure in the pulmonary artery must be lowered as well as that in the aorta.

From all this it is evident that when insufficiency of the mitral valves appears there is either a constant stagnation of a certain amount of blood in the pulmonary circulation together with the systolic regurgitation of an additional quantity, or when the ventricle accommodates itself to the reception of the increased amount of blood from the auricle merely a systolic regurgitation of a certain amount of blood. At the systole both right and left ventricles force blood into the pulmonary circulation from opposite ends and at the end of the systole the blood is under some tension, a sufficient tension to distend the elastic wall to accommodate the amount of blood in excess of normal. It is seen that as was clearly pointed out by von Basch, the situation is dependent upon the activity of the left ventricle, the right ventricle being powerless to do more than furnish its quota of blood to keep pace with the left ventricle. It has the task of forcing a quantity of blood never in excess of the normal into the pulmonary artery. In those instances in which there is a constant stagnation of blood there, it does this against a constantly increased tension. In case the conditions are such that in diastole the left auricle is able to empty itself, there will be no excessive resistance to the entrance of blood into the pulmonary circulation until that moment when (both ventricles simultaneously pouring blood into those vessels) the amount of blood exceeds the amount normally accommodated there. Then both right and left ventricle would feel the increased resistance simultaneously were the walls of the pulmonary vessels rigid. In the elastic vessels, however, the elevation of pressure is transmitted from each end in the form of a pulse wave and the resistance is felt when this wave reaches the opposite end.

In the human being insufficiency of the mitral valve with regurgitation is generally associated with other changes in the heart, which complicate the effects produced, but the results of uncomplicated mitral insufficiency are as a rule dilatation and hypertrophy of the left ventricle, chronic passive congestion of the lungs, hypertrophy of the right ventricle and if muscular insufficiency of the heart wall ensues a chronic passive congestion of the systemic veins. The problem which offers most difficulty lies in the explanation of the hypertrophy of the right ventricle and as to this there has recently been some discussion.

From any or all of the conditions indicated above it is readily seen that no matter what the character of the mitral

insufficiency, any approach to a normal circulation is only to be maintained by the increased activity of the left ventricle which receives an increased amount of blood and ejects it against a pressure which is not diminished. Sufficient explanation of its hypertrophy and dilatation is given in this statement.

As to the hypertrophy of the right ventricle the explanation is less simple. It has been said that the right ventricle throws into the pulmonary artery an amount of blood which in most instances of mitral insufficiency is less than normal and cannot exceed the normal unless by a great increase in the total amount of blood, and by great activity on the part of the left ventricle. In order to produce hypertrophy of the ventricle therefore the resistance opposed to the ejection of this amount of blood must be increased and the cause for this increased resistance we must seek in the stagnation of blood in the pulmonary circulation and in the systolic regurgitation of blood from the left ventricle.

The presence of the stagnant blood offers resistance to the entrance of more blood when the sum of the two exceeds the bulk of the blood normally received by the pulmonary circulation. To these there is always added, however, the regurgitated blood and in every instance the sum of the three is sufficient to overdistend the pulmonary vessels. As Volhard has pointed out, therefore the elasticity of the wall of the auricle and of the pulmonary vessels has a direct bearing upon the extent of the resistance opposed to the right ventricle.

If now just before systole the pulmonary circulation contains no more blood than normally present there, the hypertension will appear at that point in the systole when the distension becomes greater than that normally present at the end of systole. The same thing is true if there is already an excess of blood there, but the condition of hypertension will begin sooner and occupy more of the period of systole. We can imagine a condition in which the amount of blood in the pulmonary circulation might be so great that even at the outset of systole the normal maximum tension is overreached. Such a condition is, however, far more probable in mitral stenosis than in mitral insufficiency. The cause for hypertrophy of the right ventricle exists therefore in different cases for different lengths of time during the systole, the duration of the hypertension being longer when there is a constant excess of blood in the pulmonary circulation than in the case in which only the normal amount remains there after diastole and hypertension begins only when nearly all of the blood forced in by the right ventricle and regurgitated by the left is added to it. All this would be strictly true were the pulmonary circulation composed of a rigid tube in which equalization of pressure would occur at once.

It is seen that the condition of maximum tension is reached only toward the end of systole and since we are dealing with an elastic tube and not with a rigid one the question arises as to the rapidity of equalization of the pressure throughout, for we may imagine a condition in which the length and great elasticity of the tube connecting the two ventricles is such that the effect of the synchronous systole of both is to send waves of heightened pressure from each end which require a considerable time to reach the opposite end. Further the size of the capillaries of the lung and the friction of the passage through them might be supposed to affect the passage of the waves of pressure. We may even imagine a condition in which the length and elasticity of the tube are such, and the modification produced by the resistant capillaries in the center such that the task of the right ventricle during its systole consists practically in the distension of the pulmonary artery while the regurgitation of the blood from the left ventricle distends during systole the pulmonary veins, the equalization of the pressure occurring only after the pulmonary valves are closed and the systole over, so that the effect of the regurgitation in elevating the pressure is never felt by the right ventricle.

It will be shown, however, that the pulmonary capillaries are so wide that they may be practically neglected and the pulmonary circulation regarded as one elastic tube and it is then only necessary to determine its length and time occupied in the equalization of pressure throughout it.

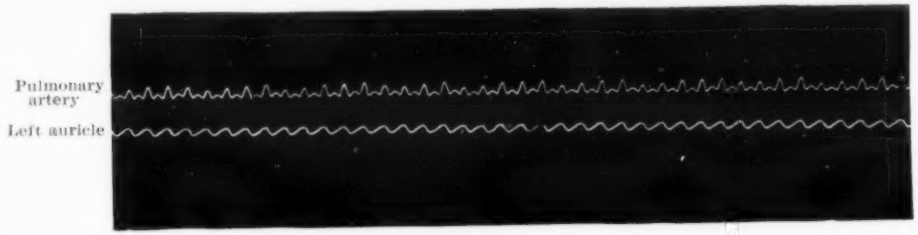
Jürgensen and Sahli and more recently Gerhardt have expressed the opinion that the hypertrophy of the right ventricle may be largely due to the direct shock from the systole of the strong left ventricle. Jürgensen makes the statement that the normal blood stream which is thrown into the left auricle from the pulmonary artery and the reflux wave from the left ventricle must, since the systole is synchronous, interfere with one another. The two ventricles work directly against one another and part of their force is spent uselessly. This does not seem to be a precise way of expressing the condition of things, for the work of the right ventricle consists not exactly in moving the blood into the left ventricle but in injecting it into the elastic pulmonary vessels where it begins its motion into the left ventricle at the beginning of diastole—a motion produced essentially by the right ventricle but in part maintained by the elastic contraction of the vessel walls and the muscular contraction of the left auricle. The pause is so short that the pressure has not time to become equalized throughout the distended pulmonary tract, but a wave travels along distending the tube as it passes. Such a wave represents the force imparted to the particles of blood by the right ventricle which are in turn communicated to those in front of them and on all sides. The particles pushed laterally stretch the vessel wall which again contracts and returns part, at least, of the energy to be transmitted again to the particles in the center and added to the impulse to go forward; thus continually losing by the energy needed to distend the elastic wall the impulse travels on, the particles moving only in a certain orbit as far as the effect of the wave is concerned. At the end of the tube the impulse is exerted in distending the wall and is returned in such a way that the wave starts back again. If such a wave meets another wave coming in the opposite direction, the energy at the point where they meet will be applied to the

elastic walls and since the particles move easily upon one another there will be little effect other than the dispersion of these particles and the great distension of the elastic walls. The elevation of pressure produced by the systole is not an instantaneous one, and the reflux wave on meeting the advancing one unites with it in its effect in distending the vessel, the maximum distension being produced at the point where the crests of the waves meet. If now these waves reach the opposite ends while the ventricles are still contracting, it is plain that the tension of the wall against which they discharge the last of their content of blood is greater than normal. If any work is wasted, it is in the unnecessarily great distension of the pulmonary vessels and not in opposing the shock from the left ventricle. This presupposes that the tube is so short that the wave from the right ventricle is still being formed when the van of the other reaches the right ventricle. If the tube were much longer there might be a lower pressure in the artery after the departure of the wave from the right ventricle when the wave from the left ventricle arrives, so that at each end of the tube there would be felt at the moment of its arrival only the distension produced by that wave. Jürgensen and Gerhardt made no experimental study of the conditions of which they speak, but it is possible to record the pressures so that the actual happenings may be studied. One may study the pressure relations by the aid of mercury manometers, but the character of the pulsations and the time relations are of course best studied by means of the Hürthle manometer or small tambours connected with the canulas by lead pipes and each moving a lever.

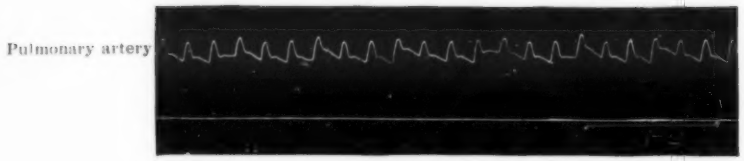
If now one adjust canulas suitably arranged in the carotid or femoral artery, in a branch of the pulmonary artery, and in the left auricular appendage and record a curve of the normal relations, the canula in the left auricle may then be removed for a moment, the hook introduced and mitral insufficiency produced and the canula replaced and tied in.

The results as compared with normal may be seen in the curves appended. The pressure rises in the left auricle slightly and there is a great pulsation, the waves being synchronous with the contractions of the left ventricle. In different cases the effect upon the pulmonary artery may vary slightly, but when the insufficiency is great and the pulsation of the auricle consequently great, the pulsation in the pulmonary artery assumes the same character (Curve 2). The pressure in the femoral artery in extreme insufficiency is greatly lowered and in these cases that of the pulmonary artery is also lowered. If, however, the left ventricle is stirred up to extreme effort, the arterial pressure may be brought up and with it that of the pulmonary (Curve 3). Now in order to explain the effect upon the pulsation in the pulmonary artery of the mitral insufficiency a canula from a fourth manometer was inserted into the severed end of a branch of the pulmonary artery toward the lung so as to receive any possible reflux wave which may have passed through its capillaries. The result is shown in Curve 4, in which it is seen that while before the insufficiency this manometer registers zero pressure and no pulsation, the pressure rises at once on the production of the insufficiency and pulsations of the character of those in the left auricle are seen. It is obviously therefore the addition of these pulse waves to those from the right ventricle in the pulmonary artery which produces the peculiar pulsation seen in that vessel. This shows further that the pulmonary capillaries offer practically no resistance to the passage of a pulse wave, a fact which is sufficiently evident to anyone who will inspect a pulmonary vein which pulsates actively, and is shown clearly by merely inserting a canula into a pulmonary vein when the pulsation from the right ventricle is recorded practically unchanged. In such curves, however, it is difficult to determine more than the gross effect of the reflux pulse on account of the inertia of the mercury, and from what was said above it is necessary to decide whether this reflux wave merely increases the height of the normal pulmonary pulse wave or is added to it as a shoulder or separate wave, in other words to observe the length of time it requires to traverse the length of the pulmonary vessels.

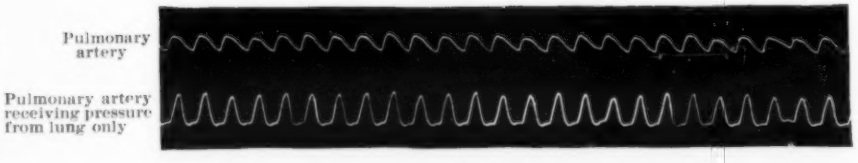
Canulas attached to tambours were therefore inserted into the left auricle and the pulmonary artery as near the heart as possible and the pens adjusted to write precisely in one vertical line. Curve 5 shows the result of this. It is seen that while the crest of the wave in the auricle is precisely synchronous with that of the higher wave in the pulmonary there is a second small wave following these higher elevations, and evidently the effect of the reflux wave which requires a little time to reach that end of the pulmonary vessel. To make this clearer the canulas were put side by side pointing in opposite directions in the cut ends of a branch of the pulmonary artery, so that one would receive the reflux wave only while the other recorded the combined wave. Curves 6, 7, and 8 show the result of this experiment in which it is seen that while in Curve 6 in the normal animal the pulmonary beats have a sharp rise and fall, after the mitral insufficiency is produced and the reflux wave appears, the fall in the pulmonary wave is not so rapid, but is delayed by a sort of shoulder which is seen to be exactly synchronous with the apex of the reflux wave taken as it will be remembered at practically the same spot (Curves 7 and 8). The exact representation of the interval in this curve required by the reflux wave to travel from the left ventricle to the arterial end of the pulmonary tract is shown in Curve 9, in which the upper curve is drawn by the pen from the left auricle while the lower is from the distal portion of the cut pulmonary artery, from the same case and with the drum running at the same speed as in the Curves 6, 7, and 8. The question still remains as to whether it can be said from these curves that the elevation of pressure from the reflux wave is felt at the root of the pulmonary artery, *i. e.*, by the right ventricle before the pulmonary valves close. It is fairly clear that this may be answered in the affirmative since it is seen that the reflux wave begins to arise before the pulmonary wave has quite



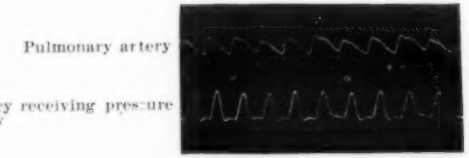
Curve 5.



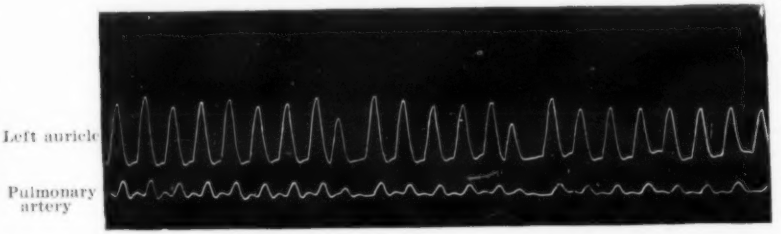
Curve 6.



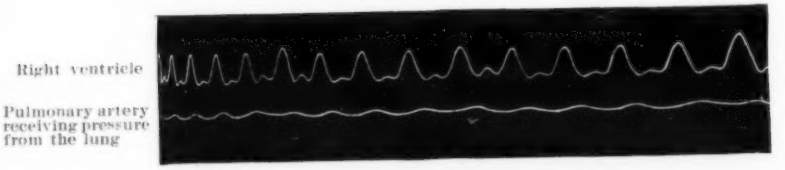
Curve 7.



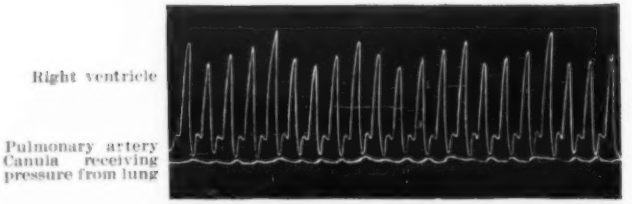
Curve 8.



Curve 9.



Curve 10.



Curve 11.

reached its climax, but it was thought that it would be clearer if it were possible to trace a curve from the cavity of the right ventricle simultaneously with one from the distal portion of the cut pulmonary branch, *i. e.*, one showing the reflux wave alone. For some reason we had great difficulties with this, but the curves finally obtained are fairly clear and show (Curves 10, 11) that the elevation from the reflux wave begins before the ventricle has finished its systole and therefore before the pulmonary valves close.

From all of this it is seen that there is less cause for hypertrophy of the right ventricle in pure uncomplicated mitral insufficiency than in mitral stenosis or in mitral insufficiency associated with myocarditis or other causes for inadequate work of the left ventricle. The cause in those cases in which the regurgitation and the activity of the left ventricle are such that there is a constant residuum of blood in the pulmonary vessels greater than normal, consists in the rapid rise in tension during systole to a point above the maximum normal tension such that an excessive effort is required on the part of the right ventricle. In this case there is the additional influence toward the end of systole of the increased tension produced by the reflux of blood from the left ventricle, the effect of which is felt by the right ventricle before the end of its systole. Even when there is no constant residuum of blood in the pulmonary circulation this hypertension due to regurgitation is felt toward the end of systole.

ACUTE HÆMORRHAGIC PANCREATITIS FOLLOWING OBSTRUCTION OF THE BILE PAPILLA.

By C. H. BUNTING, M. D.,

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In his monograph on "Diseases of the Pancreas," Opie has emphasized the importance of cholelithiasis as a factor in the causation of acute hæmorrhagic pancreatitis and has clearly demonstrated the mechanism by which a gall stone may bring about this lesion of the pancreas. There are several conditions which must be fulfilled before this may occur. The anatomical arrangement must be such that the duct of Wirsung is the main duct of the pancreas and it must join the common duct so as to form an ampulla of Vater whose length is greater than the diameter of its orifice at the papilla—a condition which is present in about three out of ten individuals. The stone must be of such size that it may close the orifice of the ampulla and not at the same time that of the pancreatic duct, thus converting the bile duct and pancreatic duct into a single closed channel. With a greater pressure in the common duct, bile may then be forced into the pancreatic duct and by its irritative action set up an acute inflammatory reaction.

This mechanico-chemical theory of acute pancreatitis, Opie bases upon the autopsy findings in which the above conditions were fulfilled—a stone 3 mm. in diameter blocking the orifice of an ampulla which measured 10 mm. in length—and in which bile was found in the pancreatic duct; also upon the experimental proof that bile injected into the pancreatic duct of animals under sterile precautions will produce the lesion of acute pancreatitis; and upon the frequency with which cases of acute pancreatitis occur in people who give a history of biliary colic or are found to have gall stones in the gall bladder or common duct at operation or autopsy. In the reference cited Opie quotes in addition to two cases of his own 39 others in which cholelithiasis was present, in eight stones being found in the common duct, in one in the duodenum, and in the others in the gall bladder, though in ten of these jaundice suggested the recent passage of a stone with temporary obstruction of the duct. In a more recent paper[1] in summarizing the evidence for this view he expresses the opinion that cholelithiasis is the usual if not the only cause of acute hæmorrhagic pancreatitis; and concludes that "whenever a biliary calculus passes through the diverticulum of Vater into the duodenum the pancreas is subjected to the danger of injury, the character and extent of which are dependent on the size of the calculus and the duration of its impaction."

Little of value has been added by subsequent work save the important demonstration by Flexner[2] that the bile salts are the constituents of the bile which produce the inflammatory reaction in the pancreas while the colloid constituents have a protective action. Acute pancreatitis was produced in dogs by the injection of a sterile solution of sodium taurocholate.

In view of the clinical and especially the experimental evidence it is difficult not to accept the theory of pathogenesis of the disease proposed by Opie and quite impossible to concur in the opinion of Robson,[3] who, though recognizing the importance of cholelithiasis in the production of the lesion, says, "For my own part I believe that infection is the important factor and that the bile is simply the conveyor of infection."

Although numerous cases of pancreatitis in which the connection with cholelithiasis has been established have been published since the work of Opie, I have been unable to find any in which at operation or postmortem a stone was found blocking the orifice of the ampulla and in consequence desire to record the following case in which there was definite obstruction of the orifice of the papilla and, though through an error in technique, the obstructing mass was lost, there is little doubt but that it was a biliary calculus.

The patient was a well nourished white man, 51 years of

[1] Journal of the Am. Med. Association, 1904, xliii, 1102.
[2] Journal of Experimental Medicine, 1906, viii, 167.
[3] Lancet, 1904, i, 845. Montreal Med. Journal, 1904, xxxiii, 741.

age, an inmate of the Bay View Almshouse, who had had not infrequent attacks of epigastric pain with some constipation usually easily relieved. On January 25, 1906, he was seized with intense pain in the epigastrium, became collapsed and showed considerable abdominal distension. On a diagnosis of intestinal obstruction he was explored; some peritoneal adhesions were freed, and the wound closed. There was no generalized fat necrosis to attract attention to the pancreas and the condition of that organ was not determined at operation. The patient died at six o'clock the following morning and the postmortem examination was made five hours after death.

The examination showed beside numerous chronic lesions, as may be seen from the appended anatomical diagnosis an acute hæmorrhagic inflammation of the pancreas, which was large, swollen and mottled with red areas of hæmorrhage and opaque yellowish areas of fat necrosis. The gall bladder was large, distended and tense with bile, and the bile ducts were also dilated and firm to the touch, clearly showing that there was an obstruction to the outflow of bile. With gentle pressure there was no escape of bile from the papilla but with increased pressure there was a sudden spurt of bile carrying before it a small yellowish white mass which was distinctly seen in transit but was not recovered from the material in the abdominal cavity in which it fell. On opening the bile duct a small stone about 2 mm. in diameter was found in the apex of the ampulla close to the orifice and in the gall bladder and cystic duct there were about 400 soft, light colored cholestrin stones, varying in size from 0.5 to 6 mm., so there seems little doubt that the escaped mass was another stone, or a stone with mucus and desquamated epithelium. Whether or not the mass was a stone there was definite obstruction and the anatomical relations of the ampulla and ducts were such that the obstruction of the orifice set in progress the mechanism described by Opie, and resulted in retro-injection of bile into the pancreatic duct. The duct of Wirsung joined the common duct 11 mm. from the tip of the papilla and on dissection was found dilated and bile stained for 4 cm. from its orifice. The duct of Santorini was obliterated at the duodenal wall and opened into the duct of Wirsung. The common duct was dilated and somewhat hypertrophied and this in connection with an induration of the pancreas seemed to indicate that the previous attacks of pain of the patient were referable to the passage of other gall stones, some of which may have been of sufficient size to block the pancreatic duct in transit and thus cause atrophy of the parenchyma and the chronic interstitial process.

The anatomical diagnosis and that portion of the protocol which is of interest from the standpoint of this paper follow:

AUTOPSY 2664. *Anatomical diagnosis.*—Cholelithiasis, with stone in the ampulla of Vater; chronic interstitial pancreatitis; acute hæmorrhagic pancreatitis; peri-pancreatic fat necrosis; exploratory operation; acute fibrinous peritonitis; cloudy swelling of viscera; emphysema; chronic bronchitis; broncho-pneumonia; arteriosclerosis; chronic fibrous myocarditis; cardiac hypertrophy and dilatation; chronic passive congestion of viscera; atrophic scars in kidney cortex; hypertrophy of prostate; hydronephrosis; chronic interstitial orchitis; chronic gastritis; round ulcer of the pylorus.

The body is that of a well nourished white man 173 cm. in length. The left leg has been amputated through the lower third of the thigh and shows old pale fibrous scars on the stump. Rigor mortis is well marked; pupils are equal and moderately dilated. The face shows marked suffusion. The abdomen is prominent and shows in the mid-line a surgical incision extending for about 10 cm. below the umbilicus and closed by through and through silver sutures. The panniculus adiposus is well developed. On opening the peritoneal cavity there is found a small amount of blood-stained fluid in the neighborhood of the operation wound, the parietal peritoneum is injected and shows numerous small ecchymoses and the intestines are lightly adherent to each other by a slight fibrinous exudate.

Pancreas.—The pancreas is large, swollen, firm and mottled in color. Across the middle of the body it measures 45 mm. in width and 23 mm. in thickness. Over its surface in the peripancreatic fat there are numerous small irregularly shaped opaque yellowish areas, evidently areas of fat necrosis. Similar areas are found in the fat at the base of the mesentery. Several small dark red areas of hæmorrhage are also found in the peri-pancreatic fat. On section of the pancreas it is found infiltrated with adipose tissue separating the parenchymatous lobules somewhat. The latter in general are more homogeneous than normal and are firmer to the touch save in some small dark grayish areas which are softened. The parenchyma of the tail of the organ appears more indurated than that toward the head. Throughout the organ but especially marked toward the head there are numerous small irregular areas of hæmorrhage, and opaque yellowish areas of necrosis similar to those seen upon the surface. Toward the middle of the body there is one grayish black area about 1 cm. in diameter which is softened.

Bile passages.—The gall bladder and bile ducts are found tense and much distended; on gentle pressure bile does not flow through the papilla into the duodenum, on increased pressure, however, there is a sudden spurt of bile carrying before it a small yellowish white mass. (This mass was unfortunately lost in the body cavity). On opening the common duct it is found filled with thick greenish bile, and at the tapered summit of the ampulla of Vater is a small gall stone between 2-3 mm. in diameter and a small amount of mucoid material. On opening the duct fully it is found to measure 17 mm. in width, in its lower portion and 19 mm. just below the junction of the cystic and hepatic ducts. Eleven mm. from the papilla the pancreatic duct enters. On dissecting out the duct of Wirsung it is found to be somewhat dilated, measuring 12 mm. across when opened; and to be bile-stained for 4 cm. above its junction with the common duct. It is joined by the duct of Santorini which tapers toward the periphery of the gland and is obliterated at the duodenum. The gallbladder and cystic duct contain many small calculi which are on section white, crystalline, quite soft and evidently composed almost entirely of cholestrin. They vary in size from 0.5 mm. to 6 mm. and are about 400 in number.

Microscopical Examination of the Pancreas. Sections made at various portions show islands of parenchyma separated by fat cells. In these islands the lobules show an increase in fibrous stroma about them, with some invasion of the lobules. The acini are in most places well preserved. The most striking features in the microscopical sections are the extensive necroses of the fat and interstitial tissue in some areas including also areas of the parenchyma. In these areas nuclear stain is entirely lost and the architecture of the tissue can just be made out. Small extravasations of red blood cells are also present in the sections both in the interstitial and fatty tissue, normal and necrotic, and between almost normal acini. In many places there is exudation of leucocytes, especially on the edges of the areas of hæmorrhage and necrosis, and many of them show fragmentation of their nuclei.

SO-CALLED SPONTANEOUS FOCAL MYOCARDITIS AND THE OCCURRENCE OF CALCIFICATION OF THE DEGENERATE MUSCLE FIBRES.

By Ernest K. Cullen, M. B.,

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(*From the Pathological Laboratory of the Johns Hopkins University and Hospital.*)

Focal changes affecting the muscle fibres of the heart are usually secondary to sclerosis of the coronary arteries but may occur in association with various infectious diseases, notably diphtheria, typhoid fever, and scarlet fever. The lesion in the infectious diseases is usually characterized by a fatty or albuminous degeneration of the fibres, hyaline degeneration being occasionally present, together with a variable increase of cellular elements in the interstitial tissue. In rapidly fatal cases the lesion, if present, is prone to be diffuse in type, while in those of longer duration the focal character is prominent. This has been confirmed experimentally by Mollard and Régaud.

In the early discussion of myocarditis in the infections diseases, considerable controversy arose as to the nature of the degenerative process. Romberg maintained that the changes in the interstitial tissue were primary, the muscle fibre being secondarily affected. Ribbert took the opposite view, considering the muscle fibre the seat of primary change, with subsequent inflammatory alterations in the connective tissue. He based his contention on the fact that in the earliest stages of diphtheria the muscle fibre was alone affected. Subsequent observations have favored Ribbert's view.

The experiments of Babes, of Welch and Flexner, and of Mollard and Régaud, have shown conclusively that the ætiological factor in the production of myocarditis in diphtheria is the toxin and not necessarily the bacillus itself. This was determined by the injection into animals of the sterile filtrate of diphtheria cultures. Similar myocardial changes have been experimentally produced with several toxic substances of organic origin.

Ziegler has expressed the view that fibrous patches in the myocardium are not always due to arterio-sclerosis, but in some instances are the result of intoxication, with consequent replacement of the degenerative fibres by scar tissue. Romberg adheres to this view. Basing his opinion upon a case following typhoid fever, in which the vessels were unaffected, he maintained that definite sclerotic changes may be produced in the myocardium, thus concluding that arterio-sclerosis is not the sole cause of fibrous myocarditis.

Calcification: The occurrence of calcification in certain pathological conditions, especially in arterio-sclerosis and myoma uteri is comparatively common. Calcareous deposists are also found occasionally in the skeletal muscles of animals, but involuntary muscles, except of the arteries, appear to be rarely affected.

Weigert has conclusively shown that calcium salts are never deposited in living tissues. In recent studies on the microchemistry of calcification Klotz has observed that in pathological processes the deposit of calcium salts is preceded by fatty degeneration of the affected tissues. The ætiology and pathogenesis of calcification have been summarized in the paper of Aschoff and the recent experiments of Klotz have shed much new light upon the process.

Two cases of calcification occurring in the cardiac muscle fibres have been reported by Coats, and single cases by Jacobsthal, Heschl, Roth, Köster, and Langerhans. Liebscher has reported a case of multiple disseminated calcification co-incident in the myocardium, liver, and spleen, but no reference is made to the microscopical picture.

The interesting feature of the case to be presented is the focal distribution of the calcium deposits in groups of muscle fibres, the fibres in most instances being still recognizable. The changes in the interstitial tissue form an inconspicuous part of the microscopical picture.

Case I. Gynecological No. 77. Pathological No. 69.

Clinical history.—Jane Johnson, colored, single, age 28, admitted into the service of Dr. Kelly on January 6, 1890. The following is an abstract of the clinical history.

No satisfactory history can be obtained from the patient, who exhibits much hebetude. She first noticed a tumor in the abdomen about four years ago. This tumor has gradually increased in size.

Physical Examination.—Pulse is 100 and regular, the radial artery seems atheromatous. The abdominal wall is uniformly rounded out by a large tumor mass which on palpation presents two small nodules in the lower abdominal zone. The vagina is large and the cervix is high up, being on a line with the superior strait. The mass is entirely out of the pelvis. A slight, exceedingly fetid, discharge is present in the vagina.

The patient was examined by Dr. Osler, who found nothing abnormal, other than symptoms resulting from upward pressure upon the thoracic organs.

From January 6, the date of admission, until January 18 the patient's condition showed comparatively little change, the pulse beat ranging from 84 to 124 per minute, and the temperature from 98° F to 99° F. On admission the urine contained a small amount of albumin. Two weeks later pus cells were found and the albumin was increased in amount. From this time on the temperature ranged between 102.3° F and 100.5° F. The patient became gradually weaker and died on January 31.

The autopsy was performed by Professor Welch on February 1, 1890.

Anatomical Diagnosis.—Myoma of the uterus with central necrosis, pyonephrosis due to pressure on the ureters, chronic

passive congestion of lungs, displacement of diaphragm and abdominal viscera by pressure of the tumor, marasmus, hypertrophy and hyaline degeneration of the heart.

The body is emaciated. The abdomen is distended by a large tumor which is quite smooth except for two nodular masses in its lower portion. The diaphragm on the left side is on a level with the second inter-space and on the right side reaches to the third rib.

The pericardial cavity contains a few cubic centimetres of clear fluid.

Heart: The heart is slightly enlarged and weighs 245 grammes. The pericardial surfaces are smooth. Fluid and coagulated blood are present in both sides of the heart. With the exception of a very slight contraction of the mitral orifice, the valves appear competent and normal. A few pale patches are seen scattered throughout the endocardium. The wall of the left ventricle measures 17 mm. and that of the right 4 mm. in thickness. The heart muscle is tolerably firm and dark brown in color. On tangential section of the left ventricular wall small yellowish foci are visible immediately beneath the endocardium. The orifices of the coronary arteries are dilated.

Lungs: The anterior borders of both lungs are emphysematous. The remaining parts of both lungs show the picture of chronic passive congestion.

Liver: The liver is rather small, the surface is smooth and shows a mottling of dark brown and yellowish colored areas. The same appearance is seen on section. The gallbladder is normal in appearance.

Stomach: Intestines and pancreas appear normal.

Kidneys: The left kidney measures 17x7x5.5 cm. The pelvis is enormously dilated and turned towards the front. The capsule is adherent and the surface irregular and lobulated. Beneath the capsule are numerous small white colored foci.

Throughout the kidney are purulent foci, the pus following lines running from pelvis to cortex. The pyramids are flattened. The pelvis is generally smooth, but here and there is covered with a fibrino-purulent exudate. The ureters are dilated and closely adherent to the posterior surface of the tumor. The dilatation extends to the point of attachment to the tumor.

The right kidney is about the same size as the left and presents essentially the same features.

The adrenals are apparently normal.

Uterus.—The uterus is 19 cm. in length, is antiflexed and occupies the anterior portion of the tumor. The ovaries are flattened. The tubes are both patent till lost in the tumor mass.

Tumor.—The tumor is nodulated and divided into two distinct lobes corresponding to either side of the vertebral column. It is quite firm in consistence. On section it presents towards the center a triangular cavity which at its base measures 11 cm. This cavity is filled with a slightly blood-stained fluid and dense masses of firm white elastic tissue. Sections from these masses show perfectly preserved muscle fibres more refractive and clearer than those in other parts of the tumor. Sections from the tumor itself show a large amount of fibrillar connective tissue between the bands of muscle fibres.

Lymphatics.—The lymphatics in the lower part of the abdomen are greatly dilated and contain a faint yellow colored fluid. The lymph glands are small.

Bladder.—The mucous membrane shows ecchymoses, is deeply injected and contains a small amount of turbid urine.

Apart from the microscopical appearance of fresh specimens of the tumor and both fresh and hardened sections from the heart, we unfortunately have no microscopical picture of the other organs as specimens were not preserved.

Microscopical Appearance of the Heart Muscle.—Scattered throughout the wall of the left ventricle, especially, near the endocardium are numerous isolated groups of opaque, deeply staining fibers which appear to have undergone calcification. (Fig. 1.) These areas are composed of adjacent fibres ranging in number usually from three to twelve. Such fibres in most instances are well defined but occasionally appear irregular in outline, as if disintegrating. They have lost both their cross and longitudinal striations and appear quite homogeneous and opaque, staining deeply blue with both methylene blue and hæmotoxylin. No nucleus of the fibre is discernible, but often small, oval or rounded nuclei are situated about the fibre. In the interventricular septum the process appears to be much less extensive. Here single fibers are observed, which present a homogeneous granular appearance and with hæmotoxylin and eosin stain differently from the surrounding fibres. Fig. 2.) Such fibres are stained faintly brown in color. The nucleus is absent. Definite calcification is, however, observed in this situation in small groups of fibres which in general appearance resemble those found in the wall of the left ventricle. In sections taken from other parts of the heart no alteration of the fibres was visible.

At the time of autopsy Professor Welch studied the microchemical reaction of those altered fibres in the fresh specimens and found on the addition of glacial acetic acid to those fibres which contained a highly refractive substance, a slow dissolution of this material without the evolution of gas. This refractive material dissolved rapidly in hydrochloric and nitric acids also without the evolution of gas. As it dissolved the fibres swelled, lost their refractive property and appeared hyaline. This substance was insoluble in strong caustic potash and ammonia. In frozen sections left over night in an aqueous solution of bichromate of potash the refractive material dissolved slowly. The most interesting reaction was observed in specimens treated with strong sulphuric acid. The refractive material changed without the evolution of gas into beautiful clumps and rosettes of narrow rhombic crystals of calcium sulphate. Similar crystals, usually single, appeared in the fluid close by. No such reactions were obtained in specimens from other parts of the heart.

Professor Welch also observed that the refractive material appeared in the form of little coarse blocks or granules, with a suggestion often of an arrangement in the line of normal longitudinal and cross striation. Fatty degeneration of the fibres close to these areas of calcifications was observed.

The connective tissue immediately in relation to these altered fibres presents a variable amount of celluar increase. In areas where only one or two fibres are involved, as in the interventricular septum, there is a very slight increase of cells while in those situations, in which the process is extensive, the number of cells is considerably larger than normal. The nuclei of these cells are oval or rounded in outline and appear slightly larger than those of the connective tissue in other parts of the section. The greater number of these resemble most closely young connective tissue cells, but a few appear

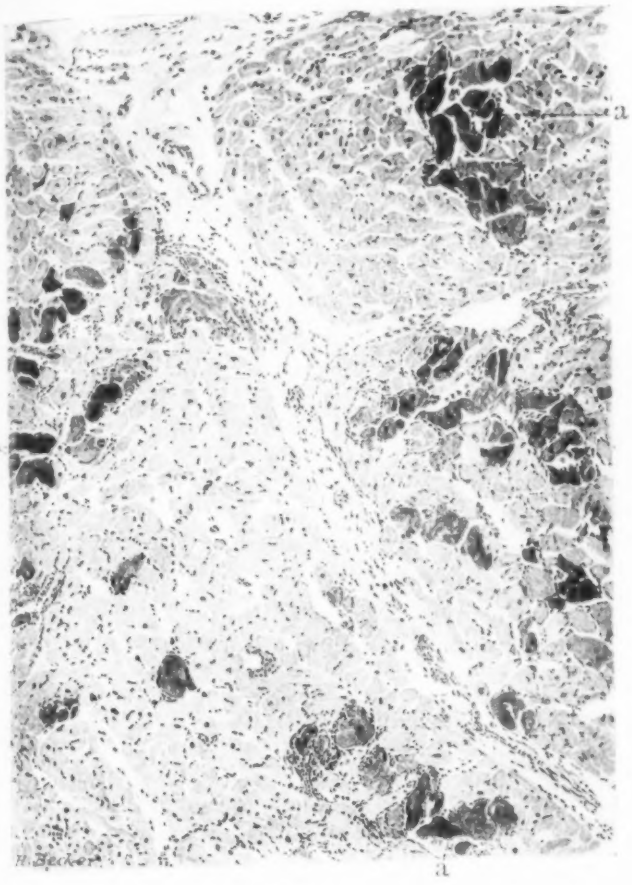

FIG. 1.

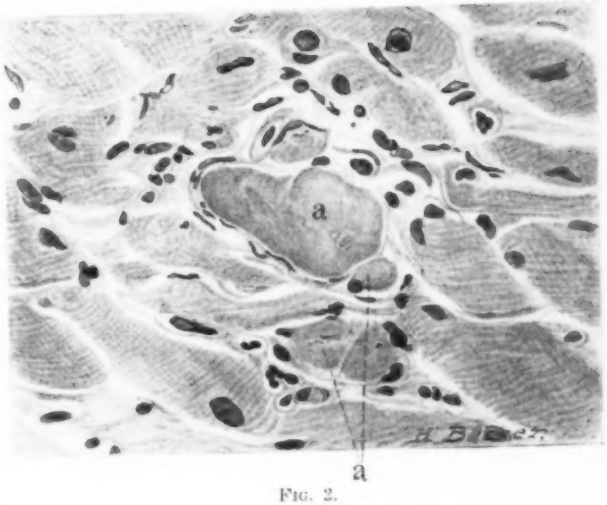

FIG. 2.

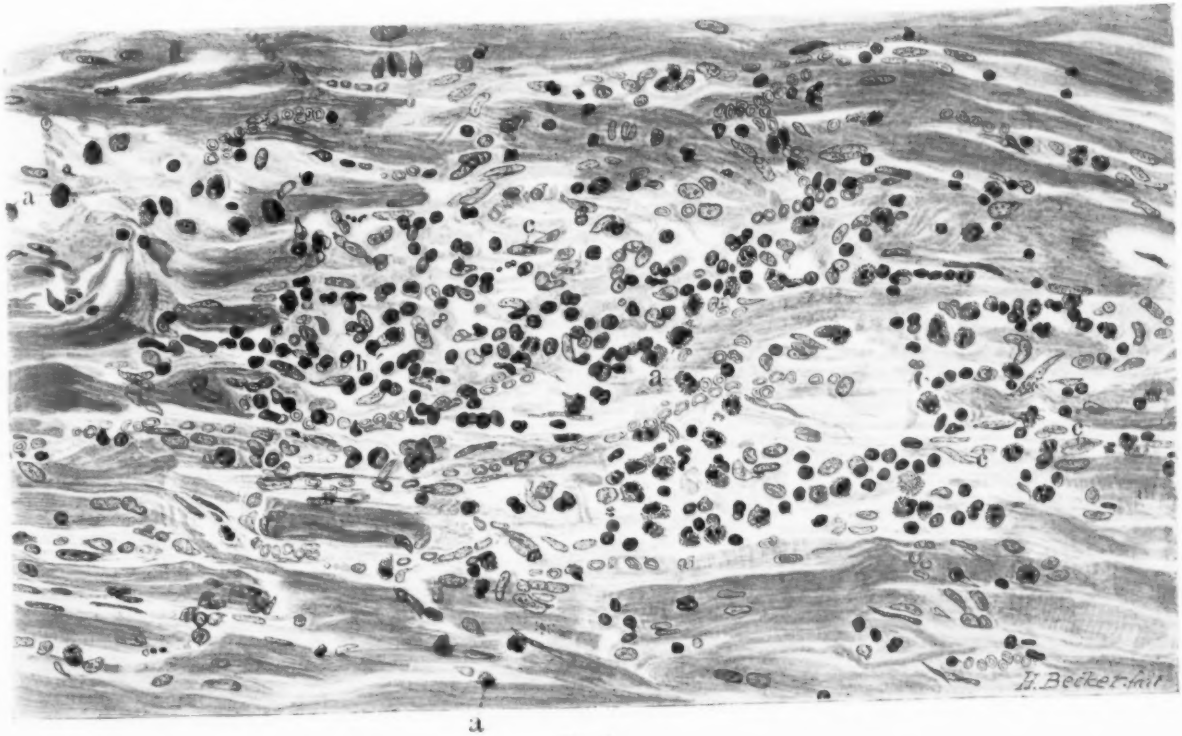

FIG. 3.

to be small lymphocytes. There is some slight increase of nuclear elements in the connective tissue not immediately in apposition to the degenerate areas. The vessels close to these foci of calcification contain a few red blood cells and some small round cells in their lumina, but there is no appreciable increase in the number of cells in the perivascular connective tissue, nor is there any evidence of alteration in the vessel walls.

The ætiology of the cell necrosis in this case cannot be definitely determined, but it is possible that the same ætiological factor concerned in the production of the existing pyonephrosis, may also be responsible for the lesion in the myocardium. The pressure exerted upon the thoracic organs by the large abdominal tumor may also have entered into the causation. This case appears to be no exception to the rule, that death of the cells precedes the deposit of calcium salts. In a study of the fresh specimens, as was mentioned in the microscopical report, Professor Welch observed the presence of fat granules in the fibres adjacent to the calcareous deposits. In hardened specimens such fibres presented a granular appearance and in some instances the typical ground glass picture was present.

From these observations it appears that a fatty degeneration of the fibres most probably preceded the deposit of calcium salts.

Acute myocarditis occasionally occurs unassociated with any other lesion, the ætiology being quite obscure. Two such cases have been reported by Freund and Rindfleisch. The patient of Freund was a man forty-eight years of age, who first complained of pain, reddening and swelling of the extremities. Symptoms of failing cardiac compensation developed and death followed in the fifth week. Microscopically the myocardium was the seat of degenerative changes in the muscle fibres with prominent cellular increase in the interstitial tissue. Freund was inclined to regard this case as belonging to the interstitial type of myocarditis.

The case reported by Rindfleisch was that of a man thirty-five years of age who fell from a height, striking on his left breast. A week later he complained of pain in the epigastrium. Cardiac distress and prostration gradually developed and the patient died at the end of the fifth week. At autopsy the heart was found to be hypertrophied and both ventricles dilated. Microscopically the muscle fibre was the seat of extensive fragmentation and the interstitial tissue was diffusely infiltrated with polymorphonuclear leucocytes, many eosinophilic cells being present.

Our second case to be presented belongs to this type of obscure origin, the so-called "primary myocarditis." Unlike the cases of Freund and Rindfleisch, the lesion is essentially focal in type. It is characterized by extensive denegeration of the fibres, accompanied by inflammatory changes in the interstitial tissue. The lesion is in no way referable to pre-existing alterations in the blood vessels, nor is there any history of existing infectious disease.

Gen. Med. No. 12,851. Pathological No. 1726. John G., age 47, German, unmarried. Admitted into the service of Dr. Osler on May 4, 1901.

Family history.—Negative.

Personal history.—Patient has been a bartender for the past four years and has used alcohol rather freely.

Previous illness.—The patient had typhoid fever several years ago.

Present illness.—For the past four months the patient has complained of a gradually progressive weakness, but until four days ago remained at his work. He has suffered considerably from cough and for some days past has complained of severe soreness down the middle of the chest. His appetite has been poor and he has suffered much from thirst. The bowels have moved quite regularly. There is no history of chills.

Physical Examination.—The patient is very weak and the face appears ashen. The radial pulse is feeble, twenty-six to the quarter and regular; the volume is small and the tension is low. Owing to his dysponea the patient has difficulty in answering questions.

The percussion note over the thorax is apparently everywhere resonant. Respiration is harsh and rather vesicular in character. A few moist râles are heard in the lower part of the axillae and posteriorily over both bases. The abdomen is soft and is free from distension. The liver and spleen are not palpable.

Immediately on admission to the ward stimulants were administered. There was temporary improvement of the pulse, but it soon became very feeble. Dyspnoea and cyanosis developed rapidly. Examination of the lungs showed a rapidly increasing oedema. The patient died two hours after admission. The chart on admission showed a temperature of 97.5° F, pulse 112, respiration per minute 30. No urine was obtained.

The autopsy was performed at 9.30 A. M. on May 5, by Dr. Opie.

Anatomical Diagnosis.—Hypertrophy of the heart with slight effusion into pericardial and both pleural cavities, oedema of lungs.

On opening the abdomen the stomach and intestines are found to be moderately distended. There is no excess of fluid in the peritoneal cavity. The left pleural cavity contains about 50 cc. of a clear straw colored fluid. The right pleural cavity contains a slightly greater quantity. Light fibrous adhesions are present over both lungs.

The pericardial cavity contains 125 cubic centimeters of a clear straw colored fluid. The pericardial surfaces are quite smooth.

Heart.—The heart weighs 445 grammes. The surface is smooth and covered by a moderate amount of fat. The endocardium is smooth. The heart muscle is pale in color and loose in texture. The wall of the left ventricle is 16 mm. in thickness and that of the right ventricle measures 3 mm. in thickness. The mitral segments show no thickening but are large and the papillary muscles are hypertrophied. There is slight thickening of the aortic segments about their bases and corpora aurantii, their free edges, however, being thin. The tricuspid and pulmonary valves are normal in appearance. The coronary arteries contain a few very slightly raised opaque patches, but the intima is otherwise smooth. The lumina are not obstructed. The aorta is smooth with the exception of an occasional raised yellow patch.

Lungs.—Both lungs are very oedematous and a few fibrous adhesions are present on their surfaces. The bronchial glands are deeply pigmented.

Apart from some slight hyperplasia of the lymphoid elements in the small intestine the other organs present a practically normal appearance both macroscopically and microscopically.

Microscopical Appearance of the Heart Muscle.—The heart muscle shows a decided change. Patches are observed in which the muscle cells have partially or completely disappeared, having been replaced by loose fibrous connective tissue, which in many instances shows an extensive infiltration with leucocytes. (Fig. 3.) The small round cell predominates, but a striking feature is the large number of eosinophilic leucocytes, which in some instances constitute the only type of polymorphonuclear leucocyte present. The septa of pre-existing connective tissue close to these areas appear œdematous and show a varying amount of infiltration with leucocytes. Coursing across the areas above mentioned may be seen capillaries containing single rows of red blood cells. The areas seem to bear no definite relation to the vessels, which themselves show no evidence of degeneration.

Adjacent to these areas of connective tissue the muscle fibres present a distinctly hyaline appearance. They stain deeply with eosin, are atrophied, very irregular in outline and often broken. The cross striation has in most instances completely disappeared, but the longitudinal is often indicated. The nuclei of the degenerative fibres vary to some extent, in size and shape, but are usually shrivelled and deeply stained. In many of these fibres occur ridges, which stain more deeply than the rest of the fibre. In several sections degenerate muscle fibres are found wholly isolated from the patches of connective tissue. About the larger of these foci there is an extensive accumulation of nucleated cells which is much less abundant about the smaller foci. The nuclei are usually oval or rounded in outline and appear larger than those of the connective tissue in other parts of the section. In some foci are found definite fibroblastic cells. Many of the cells resemble this type, but a few are observed which appear to be lymphocytes. The connective tissue not immediately in apposition to these foci shows some slight infiltration. The vessels in the neighborhood are free from any alteration. Specimens stained both for bacteria and fibrin were negative.

The lesion described above was found only in the wall of the left ventricle. Other parts of the myocardium appeared normal. The similarity of the lesion in this case to the type found in those cases associated with infectious diseases of longer duration, leads us to regard it as one of toxic origin. The lesion is limited to the wall of the left ventricle. The wall shows slight hypertrophy. As factors in the causation of this hypertrophy, valvular lesion, arterio-sclerosis and Bright's disease may be excluded. The patient was a beer drinker and possibly this hypertrophy may be similar in origin to that found in the lesion termed by the Germans "beer drinker's heart." In such hearts the hypertrophy is attributed to the increased work, consequent upon the excessive amount of fluid in the circulation.

The lesion in these two cases reported is essentially focal in character, and although the onset of fatal symptoms in each instance was rather acute, it seems justifiable to regard them as belonging to the subacute rather than the acute type of myocarditis.

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DISSEMINATED TUBERCULOSIS IN RELATION TO THE THORACIC DUCT AND VASCULAR TUBERCLES.[1]

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Since Weigert's work on the relation of tuberculosis of the blood vessels to acute miliary tuberculosis it has been generally believed that the disseminated tubercles found in various organs in cases of acute tuberculosis, were due to leakage of the tubercle bacilli into the blood stream from small vascular tubercles. Benda (1) and others have emphasized the pathology of the thoracic duct, which has been found packed with

[1] Read before The American Association of Pathologists and Bacteriologists, May 18, 1906.

tubercles or caseous material in some cases of acute miliary tuberculosis. Longcope (2) reports several such cases and mentions the fact that smears from 2 ducts which were apparently normal showed a number of tubercle bacilli. Ravenel (3) has reported interesting experiments on dogs. He fed the fasting animals with a mixture of tubercle bacilli and butter, 3½ hours later examined the thoracic duct and mesenteric glands by inoculation and demonstrated the presence of bacilli in these structures.

During the past winter the thoracic ducts in all cases of tuberculosis have been studied with regard to the presence of the tubercle bacillus. In all, smears have been made from 27 cases, including nearly every type of the disease. The method is very simple. The duct is dissected out and a small opening made in its upper portion. A slender pipette is introduced and pressure is made over the receptaculum, fluid accumulating to the amount of 1-5 drops. Smears of this fluid are stained with carbol fuchsin and methylene blue.

One may subdivide these cases for comparison into three groups.

(1) Acute miliary tuberculosis, 2 cases: Both showed ulcers in the intestines and caseation of the mesenteric glands. The smears contained many tubercle bacilli. The main vascular focus in one was a tuberculous thrombus of a pulmonary vein; in the other, a large caseating aortic tubercle.

(2) Subacute tuberculosis usually with the most extensive lesions in the lungs and numbers of disseminated tubercles in the organs. There were 19 cases in this group, of which 14 showed tubercle bacilli in smears, some only 2 or 3, others 40 or 50 on a single slide. Of these 14 positive cases, caseation of the mesenteric glands was present in all, intestinal ulcers in 11. It is of interest to note that one of these cases was at first placed in the third group, as no disseminated tubercles were seen with the naked eye, but examination of the smear showed 20 or 30 tubercle bacilli. A series of sections from the lungs, liver, and spleen showed the presence of very many minute tubercles in the very earliest stage of development.

(3) Chronic tuberculosis (usually of the lungs) with no disseminated tubercles. There was 6 cases in this group—none of which showed any bacilli in smears, 4 with tuberculous mesenteric glands, and 2 with intestinal ulcers.

From this analysis it would seem that the tubercle bacilli which are swallowed can pass through the intestinal mucosa, in some cases causing no visible lesion. The majority of these cases however showed intestinal ulceration. In their passage through the mesenteric lymph glands, in every instance, the bacilli left traces in the form of more or less extensive caseation, but the most interesting feature is that they seem able to traverse the thoracic duct with no damage to its intima.

The ducts in these series with one exception showed a smooth normal intima and delicate vessel wall. Some of the ducts appeared somewhat dilated and occasionally a little thickened, but the valves and intima were always smooth and glistening.

The one exception showed a slight constriction in its upper thoracic portion, just at the site of three of its delicate similunar valves.

A small nodule of an opaque gray color (2-2½ mm.) was situated in the duct wall just below the smooth intima and showing through it. Microscopic sections showed this nodule to be a tuberculous focus in some lymphatic tissue just outside the duct wall with extension through the adventitia. A lymphatic radicle at the margin of this area showed a small tubercle just rupturing into its lumen and the subintimal tissue of the main duct showed an infiltration with large and small round cells.

One may imagine this small lymphatic intimal tubercle as the type of many similar ones in the radicles of the mesenteric lymphatics, which are in relation to the caseating glands and from which the duct collects the bacilli which it pours directly into the blood stream.

These cases would indicate that in adults the bacilli do not pass through the lymphatic glands without causing more or less pathological change, that the bacilli can easily pass through the mucosa and lymphatic channels, but are blocked by the glands which may encapsulate them and prevent further damage (as is usually the case). On the other hand, the glands may liberate bacilli into their efferent lymphatic channels, which finally end in the thoracic duct.

Since Weigert's first description, recent methods have shown an increasing number of small vascular or intimal tubercles in cases of acute or subacute miliary tuberculosis. Ribbert (4) in a recent communication lays great stress on these small vascular tubercles as foci of distribution of tubercle bacilli. He believes that the great majority of disseminated tubercles, even in cases of acute miliary tuberculosis, are derived from these small intimal tubercles which he demonstrates by serial sections, oftenest in the lungs. In this connection a study of the development of young, rapidly growing vascular tubercles in the liver is interesting. Three cases have recently come to section in this laboratory which showed such tubercles of the portal vein. Microscopical sections show that the tubercle bacilli are oftenest deposited at he margin of the lobule, being carried there by the hepatic artery or portal vein. In their growth such tubercles naturally invade the portal veins more frequently and it is quite rare to see an invasion of the larger central veins.

The growth of such a tubercle may be outlined as follows: It soon begins to invade the wall of the adjacent portal vein, causing some accumulation of wandering cells in the middle coat and subintimal tissue. There may be some necrosis of the adventitia and infiltration of the media with the slender epithelioid cells, but the most interesting feature of this stage is the heaping up of polyblasts and small round cells below the intima, thus elevating it to some distance from the elastica interna. It is remarkable how many of these cells can accumulate below this thin layer of intimal cells before it ruptures or degenerates. A thrombus forms at once on this damaged area and closes the vessel if it is of small size, but in any case seems to wall off the young tubercle effectively from

the blood stream. If the tubercle has grown into a larger vessel one may see this thrombus form and become smoothed over by the blood current, as Benda has pointed out. The next step is most interesting and consists in a rapid overgrowth of the fresh thrombus mass, by a delicate layer of endothelial cells, and in some instances one can see an intact layer of these cells roofing over a fresh thrombus in which can be made out the lines of Zahn and fresh fibrin with no signs of organization. It is difficult to believe that these small vascular tubercles, walled off as they are by a layer of endothelial cells, can take an active part in the dissemination of the bacilli, as is held by Ribbert. It is possible that they contribute a few tubercle bacilli to the blood stream, but proof one way or the other would be very difficult, while it can be shown conclusively that in many cases the thoracic duct takes an active part in such dissemination of bacilli.

Two other types of vascular tubercle were encountered in this series and may be briefly alluded to.

(1) Intimal or implantation tubercles—may be found in any vessel—for example portal, renal, and pulmonary veins, and the aorta as well as the conus of the right ventricle. There seems to be no doubt that in the larger vessels at least, such tubercles begin by the adhesion of one or more bacilli to some part of the intima which may have been previously damaged. The subintimal tissue is invaded immediately and here the growth takes place below an intima, which usually has repaired the primary damage and presents an intact roof of thin cells covering the young tubercle. Such a tubercle may grow to a large size by the formation of a large thrombus mass, its partial organization, and then caseation. In one case there was formed in the aorta such a tubercle the size of a small pea. Even in these large tubercles there is a tendency for the endothelium to cover over part at least of the nodule by an upgrowth from its edge. (2) Medial tubercles —are not frequent but in the early stage of their development are quite definite. The bacilli are undoubtedly carried by the vasa vasorum into the middle coat; in their growth such tubercles tend to invade the lumen of the vessel, so that in an advanced case it may be very difficult to decide whether one is dealing with a tubercle which was primary in the intima with some invasion of the media, or vice versa.

Summary.—Cases of acute miliary tuberculosis usually show a vascular focus from which most of the bacilli are derived, but in the more common subacute cases with a variable number of disseminated tubercles, the thoracic duct may be the channel of infection.

Small vascular tubercles would seem not to take an active part in the dissemination of bacilli because during a greater part of their development they are covered by an intact endothelium which, if it ruptures or degenerates, is rapidly coated by a thrombus mass. This either occludes the vessel or is smoothed over, then roofed in by a rapid overgrowth of endothelium. In these cases the bacilli are usually derived from the intestine, which may or may not show ulcers. The organisms in their passage through the lymphatic apparatus give rise to caseation or tubercle formation in the glands, but usually have no effect on the lining of the thoracic duct.

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NECROSIS OF EPITHELIUM IN THE KIDNEY IN INFECTIONS AND INTOXICATIONS.

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Several cases which have been observed at autopsy in the Pathological Department of the Johns Hopkins Hospital, in which widespread necrosis of the kidney cortex was found, roused interest in this phenomenon and its relation to other lesions and the search for descriptions of similar lesions and the study of all such cases as had occurred here was undertaken under the direction of Dr. MacCallum.

The literature contains very little direct reference to any such change. What could be found more or less closely related to the process to be described was as follows:

Orth[1] mentions necrosis of the epithelium of the tubules as the result of anæmia of the tissue from various causes, obstruction of the blood-vessels by thrombi, amyloid degeneration, hydronephrosis, etc., further necroses of toxic nature in gout, diabetes, icterus, hæmoglobinuria, and poisoning with cantharidin, chlorates, chromates, petroleum, etc., and finally necroses which follow infectious diseases such as pyæmia, septicæmia, typhoid fever, diphtheria, acute atrophy of the liver, acute tuberculosis, etc.

Nearly all writers in speaking of acute and chronic forms of nephritis, mention in addition to the ordinary degenerative changes in the epithelium of the tubules the necrosis of some, at least, of the cells which may occur.

Aufrecht,[2] Israel,[3] Kossa,[4] Schmaus,[5] and others have studied

[1] Orth, Lehrb. Spec. Path. Anat., II; 1893.

[2] Aufrecht, Ctbl. f. inn. med., 1895, XVI, 241.

[3] Israel, Virch. Arch., Bd. 123, 1891, p. 310.

[4] Kossa, Ziegler's Beitr., Bd. 29.

[5] Schmaus, Atti. di. XI Kongr. med. internaz. Roma, 1894, II, 215.

experimentally the histological changes leading to necrosis of the kidney substance after ligation of the vessels, the nature of the change, its relation to coagulation, the occurrence of calcification and the processes of karyorrhexis being the points of interest.

Leutert,[6] Gebhardt,[7] Ebstein, Nicolaier[8] and others have described the severe injuries to the epithelial cells, which result from poisoning with sublimate and oxalic acid and show that calcification appears most extensively before complete necrosis is reached.

Ebstein[9] gives in his paper on diabetes with cirrhosis a plate illustrating the change in the kidneys, which consists in a general necrosis of the epithelium of the convoluted tubules.

Lorenz[10] also finds in erysipelas necrosis of the epithelium of the convoluted tubules while the straight tubules and the descending portion of Henle's loop as well as the glomeruli are preserved. So also in septic processes, while in diphtheria the necrosis, although sometimes occurring, is less intense.

Recently a few cases have been described in which extensive necrosis of the renal epithelium occurred and which have been explained on mechanical grounds.

Bradford and Lawrence[11] observed the case of a young woman who immediately after confinement developed anuria; death followed without uræmic symptoms. Thrombosis and obliterative endarteritis were found to have occluded all the smaller cortical arteries, complete necrosis of the cortical epithelium resulting.

Griffith and Herringham[12] have quite recently described a case similar in all details to this.

Zaaijer[13] describes a similar case in which anuria and death followed confinement. There was necrosis of the whole cortex of the kidney which the author thought to be due to increased intrarenal pressure compressing the vessels which were not otherwise obstructed. The anæmia resulting from this is described as the cause of the necrosis.

Practically nothing else except vague statements that necrosis may occur in the course of nephritis due to various causes could be found in the literature, and it was consequently thought advisable to collect the cases which have occurred here and attempt to determine their underlying cause. Among 2500 autopsies ten cases of this character were found and will be described briefly as follows:

CASE I.—White woman, aged 50 (Med. No. 12,577, autopsy 659). Family and personal history unimportant. For 8 to 10 years has had periods of dull pain in right hypochondrium, never any jaundice. During last two months has had several attacks of severe pain in that region and since the last one, has gradually become jaundiced. Vomiting is frequent. Stools decolorized. Died ten days after admission to hospital. *Urine* on admission showed a specific gravity of 1015, deep brown color, traces of albumen and bile stained casts.

Later the urine showed leucin and tyrosin crystals, while in the hospital it varied from 200-300 cc. per diem. Temperature was subnormal for the greater part of the time.

The patient died ten days after admission. Only the essentials from the autopsy are given.

Anatomical diagnosis.—General infection with *B. coli*. Anatomical occlusion of the cystic duct and narrowing of the common bile duct. Acute yellow atrophy (?) of the liver. Jaundice. Chronic adhesive peritonitis. Ecchymoses in intestine and stomach.

Body strongly built; deep jaundice of the skin and all tissues; hæmorrhages here and there beneath the peritoneum.

Liver.—Capsule is smooth and free from adhesions. Its surface is dark in color. The whole organ is diminished in size, weighing about 1400 gms. It is soft and when placed on the table tends to flatten out. The edges are thin. On section it is of a greenish black color, with numerous lighter areas scattered through it. The bile ducts within the liver are dilated. The gall bladder is collapsed, its coats are much thickened and it contains glutinous mucus with little or no bile stain. The cystic duct is thickened and its lumen reduced. There is a considerable dilatation of the hepatic duct. This forms a pouch the size of the thumb, which contains greenish bile, and from which bile may be expressed into the duodenum. The liver shows central areas of complete necrosis and obliteration of the structures in the center of the lobule. The peripheral liver chords are not so seriously affected but the cells are filled with numerous granules and fatty globules.

Kidneys.—Combined weight 370 grammes. Capsule strips off with ease. On section the cortex is bile stained, the striations plainly seen, the glomeruli visible as bright red points. There are ecchymoses in the pelvis. The cortex is almost entirely necrotic; the medullary portion has been fairly well preserved. The glomeruli are fairly well preserved although their epithelium seems to have suffered somewhat. The epithelial cells of the convoluted tubules are for the most part completely necrotic; at the best, they contain only deeply staining shrunken nuclei or merely a dust of black nuclear fragments. In many places the cells are broken to fragments and form a mass of granules in the lumen of the tubule. The conducting tubules are better preserved, although their cells in many places are swollen and contain deeply stained shrunken nuclei. There is no evidence of inflammatory exudate, and no new growth of fibrous tissue. In the medullary portion there are some casts.

CASE II.—Colored man, aged 22, Med. No. 32,784. Autopsy 1621. Family and personal history negative. Always well up to 10 days before death, when jaundice appeared with general malaise. Four days later he began to vomit at first a greenish material, but later a material containing altered

[6] Leutert, Fortschr. d. med., Bd. 13, 1895.
[7] Gebhardt, Inaug. Diss. Freiburg. Bd., 1897.
[8] Ebstein and Nicolaier, Virch. Arch., Bd. 148.
[9] Ebstein, Deutsches Arch. f. klin. med., Bd. 28, p. 143, 1880.
[10] Lorenz, Ztsch. f. klin. med. XV, 416, 1889.
[11] Bradford and Lawrence, I. Path. and Bacteriology.
[12] Griffith and Herringham, Brit. Med. Journ., 1905, 2, 1182.
[13] Zaaijer, Mitth. a. d. grenz. d. med. u. chir., Bd. XII, 1900.

blood. The day before his death he became delirious, passed urine involuntarily and was seized with convulsions which persisted until an hour before death, when he passed into coma in which he died.

Urine was red in color, sp. gr. 1018, reaction acid and contained some bile pigment. Much albumen present. Microscopically red blood cells, hyaline casts, epithelial cells all deeply bile stained.

The amount excreted could not be determined as the patient died a few hours after admission.

Leucocytes 25,000 on admission, red corpuscles 5,200,000. Hæmoglobin, 90 per cent.

Autopsy.—Anatomical diagnosis.—Acute yellow atrophy of the liver, jaundice, submucous and subserous hæmorrhages. Parenchymatous degeneration of the kidneys. Adhesive perisplenitis. Tuberculosis of the bronchial lymph nodes.

Body sparely nourished; skin and tissues deeply tinged with yellow. Ecchymoses over epicardium, peritoneum, etc.

Liver weighs 770 gms., flaccid in consistence. The surface is reddened, roughened by areas about 4 mm. in diameter which are reddish yellow in color and slightly raised above the surrounding deep red surface. On section the cut surface is bright yellow with a greensh tinge with alternating red and yellow patches. Gall bladder contains viscid greenish bile. Very extensive necrosis involves the whole central part of the lobule extending from one lobule to another, so that only portions of tissue about the portal veins lie isolated in a mass of collapsed necrotic material. There is a new growth of bile ducts about the original bile ducts, and the connective tissue seems increased in amount. About these portal vessels extremely little liver tissue remains preserved.

Kidneys.—About normal in size. The capsule strips off readily leaving a smooth red surface. On section the cortex averages 7 mm. in thickness and is brownish red with a greenish tint. Striations well marked. Glomeruli visible as bright red dots. Ecchymoses are present in the pelvis. Combined weight, 420 gms.

The blood-vessels are quite clear. The medullary part shows some degenerative changes in the epithelial cells. On passing into the cortex it is found that almost all the convoluted tubules while still sharply outlined are completely filled with a homogeneous granular pink staining mass, into which the epithelial cells are merged. No nuclei are to be seen, except those of the intertubular tissue. The glomeruli are quite well preserved, except that their epithelium seems to have been destroyed in many cases, while in others it is for the most part intact. The conducting tubules are still better preserved, and in their lumen, but not in those of the necrotic tubules, there are abundant accumulations of a small rounded mass of calcium salts, which take a blue stain. (This supports the results of Leutert and Gebhardt, who find that the calcium deposit takes place rather in the injured than in the already dead cells.)

The *Streptococcus pyogenes* and *B. coli* were found in the blood and in the organs.

Case III.—Colored man, aged 49. Surgical No. 38,604. Autopsy 1913. The patient complained of symptoms which led to the diagnosis of carcinoma of the stomach and an exploratory laparotomy was performed which revealed an inoperable carcinoma. After the operation the temperature became elevated and the pulse rapid and he died four days later.

Autopsy.—Anatomical diagnosis.—Adeno-carcinoma of the stomach with metastases, acute splenic tumor. Cloudy swelling of the kidneys. Stomach presents a large tumor mass involving the omentum and adjacent glands and extending beyond the pylorus into the wall of the duodenum.

Liver.—Weighs 2200 gms., measures 32 x 18 x 9 cm. On section the lobules are distinctly outlined, the periphery being gray, the centers more reddish. Gall bladder and ducts normal. The liver shows some disarrangement of the epithelial cells, some of which are shrunken. There are no definite areas of necrosis.

Kidneys.—Combined weight, 320 gms. Each meaures 11 x 7.5 x 4.5 cm. The cortex is 8 mm. in thickness. Capsule strips off with some difficulty but does not tear the surface. On section the cortex is pale and yellowish, the striations indistinct, but the glomeruli are plainly visible. The blood-vessels are clear. The cells in the pyramidal part of the kidney are for the most part preserved. In the cortex, there is most extensive necrosis of the epithelium particularly of the convoluted tubules, but this is not so advanced as in the previous cases, many tubules showing a few nuclei, while the remaining cells have none. The glomeruli and conducting tubules are much better preserved, but the epithelium of the glomeruli is much disintegrated, and at times necrotic. There is no inflammatory exudate, and no new-formed fibrous tissue. The *Streptococcus pyogenes* was found in the heart's blood; spleen and abdominal incision together with the *B. coli*.

Case IV.—White woman, aged 24. Surgical No. 48,840. Autopsy 2413. Patient was admitted suffering from extreme dyspnœa and symptoms of a severe toxæmia. The tonsils were greatly swollen and were evidently the site of an abscess. The patient was quite cyanotic and became unconscious. Tracheotomy was performed and the respiratory distress somewhat relieved, but she died without ever regaining consciousness.

Autopsy.—Anatomical Diagnosis.—Abscess of tonsils with generalized infection; Cirrhosis of liver; acute bronchitis; acute splenic tumor.

Liver.—Distinctly smaller than normal, soft and flabby with many ecchymoses. The surface is covered with projecting masses of liver substance between which there are depressions in which lie injected veins. There are old scars with regenerative changes indicating long past injuries to the liver substance. There are some hæmorrhages in the substance of these scars. There is marked hypertrophy of the remaining liver substance, but there are no fresh injuries to the liver, unless the hæmorrhages form an index to such injury.

Kidneys.—Are quite soft and enlarged, weighing 400 gms. The capsule is slightly adherent and tears the surface on removal. The surface is, however, fairly smooth and the lobulations are very distinct. On section the cortex is of about normal thickness, striations are fairly regular, the blood-vessels are injected and the glomeruli appear as bright red spots. The pelvis contains some greenish opaque fluid. Its walls are injected and there are some ecchymoses.

The tubules in the pyramidal portion show marked degenerative change, the epithelial cells containing much fat, and being disintegrated in places in the cortex. The epithelial cells of all of the convoluted tubules are quite necrotic and converted into shapeless masses of red staining material, without nuclei which have fallen off from the basement membrane. The glomeruli have lost their epithelium, but otherwise are fairly well preserved. The conducting tubules are still lined with nucleated cells. There is no inflammatory reaction. The blood-vessels are clear throughout and show no thrombi. *Streptococcus pyogenes* and *Micrococcus aureus* were found in the form of a general infection.

CASE V.—White man, aged 50. Med. No. 40,387. Autopsy 2021. Entered the hospital twenty-four hours after receiving a severe blow on the side which was followed by intense pain and dyspnœa.

Evidences of pleural inflammation soon appeared with with dyspnœa and cyanosis. Leucocytosis of 11,400, marked delirium cordis with loud systolic murmur at apex. Dulness and tubular breathing developed over the bases of the lungs and the Cheyne-Stokes type of respiration appeared. Death occurred 24 days after admission with elevation of temperature.

Urine.—Spec. gravity, 1017; color, dark yellow; acetone present; urea averaged 12 gms. daily. Patient excreted 350 cc. on admission, which diminished to 120 cc. before his death.

Autopsy.—Anatomical Diagnosis.—Fracture of 6th, 7th and 8th ribs. Sero-fibrinous pleuritis. Atelectasis of lower lobe of right lung. Acute bronchitis. Subacute fibrinous adhesive pericarditis. Chronic mitral endocarditis with insufficiency. Chronic passive congestion of viscera.

Thorax contains about 1500 cc. of turbid fluid, in the left pleural cavity. Right lung bound to the chest wall by old adhesions.

The layers of the pericardium are bound together by recent adhesions, the mitral valve thickened and shortened. Heart is enlarged, the right ventricle being especially hypertrophied.

Liver.—Weighs 1500 gms., consistence firm. Surface is smooth and on section the lobules are indistinct. There is apparently some induration of the tissue. The epithelial cells are very much swollen; capillaries are seen with difficulty between them. They are granular, contain pigment and fat lobules, but there are no areas of necrosis.

Kidneys.—About normal in size, capsule firmly adherent and strips off with some difficulty, leaving a rough surface. Stellate veins are injected. On section the cortex is of a general purplish color, the vessels are quite prominent and the glomeruli may be seen as dark red points. The cortex measures 7 mm. in thickness.

The kidney is much congested. Blood-vessesl are patent throughout. In the cortex practically all of the convoluted tubules are filled with necrotic masses of epithelium; their lining cells having lost their nuclei, and having become coalescent into a formless mass. There are patches here and there in which the cells are preserved. The conducting tubules show a lining of nucleated cells. The glomeruli are fairly well preserved, but seem to have lost their epithelium.

Cultures were unfortunately contaminated.

CASE VI.—White man, aged 75. Surgical No. 48,704. Autopsy 2439. Entered complaining of shortness of breath and cough. Had recently indulged heavily in drink. Mental derangement. On November 30, the temperature rose from subnormal to 101°, and next day constipation and retention of urine began. Afterwards until his death urine was obtained only on catheterization. Leucocytes, 8500.

Cheyne-Stokes respiration, rapid and irregular pulse. During the last few days temperature steadily rose until his death, when it was 108°.

Urine.—Spec. gravity, 1030-1034, otherwise negative.

Autopsy.—Anatomical Diagnosis.—Arterio-sclerosis; cardiac hypertrophy and dilatation with myocardial degeneration. Chronic passive congestion of the viscera; œdema of lungs; fatty degeneration of the liver. Hypertrophy of prostate.

Liver.—Slightly increased in size and weight. Its surface is slightly irregular, there being numerous depressed reddish areas separating elevated areas of light yellow. There are well marked furrows due to the pressure of the ribs. The edge is rounded and the whole organ is soft. On section the central veins are injected. The parenchyma is extremely light in color and has a greasy feel. There appears to be no increase in the connective tissue. The gall bladder is very large and distended with dark greenish bile. It contains no concretions and the bile ducts are all open. The liver shows a slight cirrhosis. The liver tissue which remains, is extremely fatty, almost all the cells being occupied by large fat globules. There are no areas of necrosis, but the scars are quite extensive throughout the liver substance.

Kidneys.—Are surrounded by a thick, fatty capsule, and weigh together, 450 gms. They are slightly enlarged; the capsule strips easily, leaving a smooth surface, which is somewhat injected. Striations are regular, parenchyma is somewhat pale and cloudy with a yellowish color toward the boundary zone. The pelvis appears normal.

The blood-vessels are patent. Some of them are greatly distended with blood. The pyramids are fairly well preserved, but some of the tubules show marked degeneration of epithelium. In the cortex all the epithelial cells of nearly all the convoluted tubules are necrotic. There are a few which still show nucleated cells. The glomeruli are congested. The epithelial cells much disintegrated. There is no evidence of inflammatory reaction; no scarring of the kidney.

Culture from the spleen, shows the *Bacillus coli* and *B. acidi lactici.*

Case VII.—Colored woman, aged 35. Gynæcol. No. 26,172. Autopsy 1353. Entered hospital April 13, complaining of hæmorrhoids and pain in abdomen. On April 20, and again on April 26, she was examined under an anæsthetic, chloroform being used on April 26. After that she grew weak and passed into coma April 29, in which she died. Temperature was much elevated before death. Urine on admission showed sp. gr. 1024, acid; no sugar; no albumen. Heavy pinkish sediment. There was no further examination of urine.

Autopsy.—Anatomical Diagnosis.—Ulcerative colitis; disseminated fat necroses. Acute atrophy of the liver.

Heart, lungs, spleen, etc., show no abnormality.

Opaque white areas were found in the fat of the omentum and mesentery about the pancreas.

Intestine shows extensive shallow ulcerations with remaining islands of mucosa.

Liver.—In general is smooth. There are a few tags of old adhesions. It is about normal in size and weight. On section it is not homogeneous. In the superficial portion the lobules are plainly marked out, the anterior being congested. In the more central portion of the liver the lobules are even more sharply marked out and present a net-work of white and yellow lines, surrounding opaque yellowish areas. The center of the lobule is pale and whitish, but toward the periphery it becomes ocher yellow. Gall ducts and gall bladder normal.

The liver shows a distinct midzonal necrosis, which causes the disappearance and coalescence of all the cells of the lobule, except those quite near the portal vessels, and those quite near the efferent vein. The remaining cells contain a good deal of fat, and show here and there mitotic figures. There is no scarring of the liver.

Kidneys.—Are normal in size and weight, the capsule strips off readily, leaving a smooth surface. On section the cortex is 6 mm. in thickness. Striations well defined and the glomeruli apparent as red dots. The cortex is rather pale. The blood-vessels are patent. The pyramidal portion of the kidney shows hæmorrhages and necrotic fragments in the conducting tubules, but the lining cells are for the most part preserved in the cortex. Many of the convoluted tubules have a well preserved lining, but many show complete necrosis of the epithelial cells. The injury is not so intense as in the preceding cases; and shadows of the nuclei at least may be seen in almost all of the cells. The conducting tubules and glomeruli are better preserved, but the glomeruli show frequently a loss of epithelium. There is no inflammatory reaction. Heart's blood, liver and kidney showed *Streptococcus pyogenes* and *Bacillus coli*.

Case VIII.—Colored woman, aged 21, Gynæcol. No. 9380. Autopsy 1879. Confinement 8 months ago, uncomplicated. Abscess developed in pelvis, which was punctured and drained, 200 cc. of pus being evacuated. February 25, the peritoneum became infected. Symptoms of general peritonitis ensued and continued in spite of operation and cleansing of abdominal cavity. Intestinal obstruction ensued and amount of urine secreted diminished greatly in amount. Continual vomiting; death on April 2. Temperature rose to 105° before death; urine examined only on admission, and on February 27, at latter date, just after operation, it showed albumen and many leucocytes and squamous cells.

Autopsy.—Anatomical Diagnosis.—Operation wounds in vagina and abdomen. General fibrino-purulent peritonitis; purulent endometritis. Bilateral salpingectomy. Sero-fibrinous pleurisy. Fatty degeneration of heart and liver.

The abundant exudate in the peritoneum and pleura need not be further described.

Liver.—Slightly enlarged, very pale and yellowish, mottled with yellowish opaque and red foci, which are also seen on the cut surface. In some areas the center of the lobule is red, the periphery yellow. Gall bladder contains dark bile. The lobules are sharply marked out by lines, throughout which the liver cells are loaded with fat. These occupy the periphery of the lobule extending from portal space to portal space. There are no actual necroses in the liver.

Kidneys.—Slightly enlarged. Capsule strips off easily, leaving a smooth surface with injected stellate veins. Cortex is 7 mm. in thickness and slightly injected. The striations are indistinct, but the glomeruli are quite prominent. The pyramidal portion is somewhat congested. The epithelial cells fairly well preserved. In the cortex all the convoluted tubules have become necrotic with the exception of a few epithelial cells, which still show faded nuclei. There is an extensive desquamation of the epithelial cells of the conducting tubules, as also of the epithelial lining of Bowman's capsule. There is no inflammatory reaction. There are some hæmorrhages throughout the cortex of the kidney. *Streptococcus pyogenes* with *B. coli* was found in all the exudates.

Case IX.—Tissue from miscellaneous collection (No. 569) probably from New York. The jar is labelled a case of acute yellow atrophy of the liver, duration of the disease one week; acute symptoms two days; mania and delirium.

Liver.—Weighed two and one-half pounds, and showed reddish brown and yellowish lobular markings. There was no liver tissue to examine.

Kidney.—The blood-vessels are patent. All the convoluted tubules show complete necrosis of the epithelium, which lies in a formless mass without any nuclei staining in the tubules. The epithelium of the conducting tubules is better preserved and contains nuclei; that of the glomeruli as well as the glomerulus itself, seems but slightly injured. The tubules are everywhere swollen and tightly packed together. There is no inflammatory reaction and no new growth of connective tissue.

Case X.—White woman in private practice of Dr. Williams. Autopsy 2110. This case which is described by Dr. Williams in his paper on "Pernicious Vomiting of Pregnancy" (J. H. H. Bulletin, March, 1906), was seen in the

third month of pregnancy; all efforts to check the continual vomiting being in vain, an abortion was performed in the hope of saving the patient's life; but she grew weaker and died a few days later.

Examination of urine a few days before death showed nothing of importance.

Autopsy.—Anatomical Diagnosis.—Laceration of vagina and cervix uteri. Adherent placenta in uterus of early pregnancy. Focal necrosis and bile staining of liver. Fatty degeneration and bile staining of kidneys. No cultures were taken. There was no peritonitis or other fresh inflammatory process.

Liver.—Decreased in size, weighs 1000 gms. It is bright yellow in color, and is quite soft. Its surfaces are everywhere smooth. On section it is bile-stained and fatty. Areas and lines of degeneration and necrosis are evident by their opacity to the naked eye. Between these areas the capillaries stand out very plainly. Gall bladder normal. The liver shows a midzonal necrosis frequently affecting also the central zone. Throughout the necrotic area, the nuclei have disappeared, or are represented by fine dust of nuclear fragments. The more peripheral liver cells are very full of fat and show very abundant mitotic figures.

Kidneys.—Increased in size. The capsule strips off readily leaving an opaque yellow surface. No vessels are to be seen. On section the cortex measures 7-8 mm. and is very yellow and opaque. No structures, vessels, or glomeruli can be distinguished in the cortex. It has a granular appearance and is slightly raised above the level of the pyramids. The pyramids are pale and their peripheries show lines of opacity.

The blood-vessels are clear. The pyramidal portion of the kidney is a little altered. The cortical portion shows complete necrosis of the epithelium of all the convoluted tubules which are still packed with the coalescent mass of pink staining granular material, in which the cell outlines and nuclear shadows are only faintly visible. The glomeruli and convoluted tubules are better preserved, and show nuclei in all their cells, even the epithelium of the glomeruli being pretty well preserved.

SUMMARY.

The cases may be summarized as follows in a table:

No.	Age.	Sex.	General condition.	Duration of illness.	Bacteriological report.
1	50	F.	Jaundice, acute yellow atrophy of liver	2 weeks	B. coli, general infection
2	22	M.	Acute yellow atrophy of liver	10 days	Streptococcus pyogenes, B. coli
3	49	M.	Carcinoma of stomach; streptococcus infection following operation	4 days	Streptococcus, B. coli
4	24	F.	Suppurative tonsillitis; generalized infection	2 days	Streptococcus, micrococcus aureus
5	50	M.	Fracture of ribs; pleuritis and pericarditis	3 weeks	Cultures contaminated
6	75	M.	Chronic alcoholism, delirium, hyperpyrexia	18 days	B. coli and B. acidi lactici
7	35	F.	Acute yellow atrophy of liver, acute enteritis	16 days	Streptococcus and B. coli
8	21	F.	Pelvic abscess; general peritonitis, pleuritis	5 days	Streptococcus and micrococcus aureus
9	21	F.	Acute yellow atrophy of liver	7 days	Streptococcus and micrococcus aureus
10	21	F.	Pernicious vomiting of pregnancy; acute yellow atrophy of liver	3 weeks	Streptococcus and micrococcus aureus

This summary makes it clear that the kidney in these cases has been affected by some poison circulating in the body whether bacterial or not, which quickly destroys all the highly specialized and sensitive epithelial cells, so quickly indeed that there has been no time for reaction of any sort. This injury to the kidney is quite analogous to those necroses of the liver which are usually classed under the name of acute yellow atrophy and indeed of the 10 cases, 5 showed also the lesions of acute yellow atrophy of the liver. Nevertheless just as in the cases of hepatic necrosis there is not always complete necrosis of the renal epithelium so herein the remaining cases in which bacterial or other toxins destroyed the renal epithelium, the liver escaped.

The changes differ obviously from those seen in acute nephritis in the completeness and suddenness of the destruction and in the lack of reaction.

ON THE GROWTH OF LYMPHATICS IN GRANULATION TISSUE.

BY T. HOMER COFFIN, M. D.

(From the Pathological Laboratory, Johns Hopkins University, Baltimore.)

The mode of growth of the lymphatics in the development of the embryo has been fairly satisfactorily worked out by Ranvier, MacCallum, Sabin and others, but there seems to be but little in the literature referring to the new formation of these channels in the course of regeneration of tissue in the adult animal. The following work was therefore carried out under the direction of Dr. MacCallum in the attempt to clear up their mode of growth in granulation tissue.

It has been shown by MacCallum in a study of the relation of the lymphatics to connective tissue that in the embryo, growth takes place by an active proliferation of the endothelial cells which constitute the complete walls of the channels and which may extend in the form of elongated rows of cells sometimes branching, sometimes sending out long lash-like processes for a considerable distance in advance of the lumen.[1] Later it was shown by Dr. Sabin that this process of growth begins in the form of buds from the endothelium of

[1] Johns Hopkins Hospital Bulletin, XIV, No. 142, January, 1903, Figs. 5, 6, and 7.

the veins which push their way radiately far and wide into the tissues of the animal, finally meeting and anastomosing with ramifications from the opposite side.[2] It seemed entirely probable that this method of growth which is in most respects similar to that of the blood vessels would be carried out in the formation of granulation tissue or indeed in the furnishing with lymphatics of any new-formed tissue, and it was determined to put it to a test in a position where such tissue formation could be easily controlled.

It is well known that it is very easy to inject the lymphatics of the wall of the intestine by inserting a hypodermic needle into the subserous tissue, and on that account the granulation tissue to be investigated was made to grow upon the serous surface of the intestine. For this purpose a loop of intestine was drawn out and sewed into a wound in the skin, only a portion of the circumference of the gut being allowed to project. In the course of a week or ten days the loop was usually found to be well covered with granulation tissue, which rendered it inconspicuous in the bottom of the wound. The animal was then killed and an injection of the lymphatics of the wall of this loop of intestine was made by plunging the needle of the syringe into the quite smooth intra-abdominal part of the loop near the line along which it adhered to the inner surface of the body wall. It was found that it is quite easy to make an injection of the intestinal lymphatics in this way and that the injection will run for a certain distance into the granulation tissue which grows upon the exposed portion of its surface. It is thus evident at once that lymphatic channels spring from those present in the original tissue and advance into the overlying granulation tissue. No difficulty was experienced in recognizing the injected vessels as lymphatics, but in some cases to make quite sure the blood vessels were first injected from the larger arteries with a mass of another color. Serial sections were then made through the intestinal walls and overlying granulation tissue.

Microscopically it was found in these sections that the original lymphatics of the intestinal wall are distended with the injection mass and that from them there spring up sprouts into the granulation tissue which resemble closely sprouting blood vessels except perhaps in that their walls are quite thin. The tips of these sprouts are represented in Figures 1-2, in which it is seen that the injection mass proceeds toward the surface between endothelial cells until the lumen of the channel narrows to a point where the injection stops. Beyond this there are continued for a short way the endothelial cells in a single or partly double row. These cells are quite plump and their nuclei are large and vesicular. Nuclei and cell bodies are seen sometimes to diverge from the line and to send forth protoplasmic processes into the adjacent tissue and the terminal cell of the advancing strand is frequently seen, as in Figure 1, to be continued into a long lash of protoplasm which reaches far forward into the tissue crevices. In this advance portion there is no lumen and it is difficult to understand exactly by what mechanism the lumen is produced unless it be by the lateral growth of the cells which may lead to their separation. It is seen here as always that the lymphatic channels are perfectly sharply outlined independent structures completely formed of endothelial cells and standing in no more intimate relationship with the crevices of the connective tissue than do the capillary blood vessels.

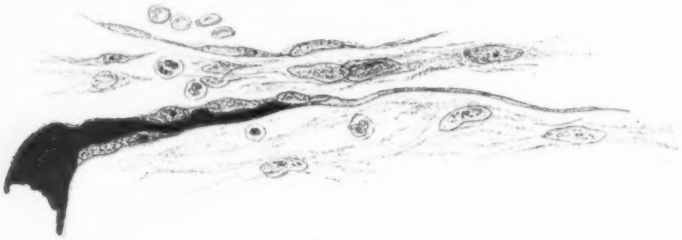

FIG. 1.

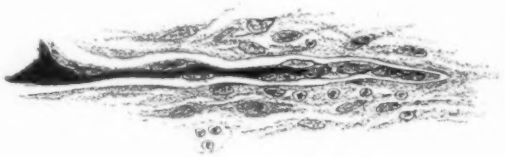

FIG. 2.

[2] Am. Journal of Anatomy, Vol. 1, 1901-2.

OBSERVATIONS ON THE GROWTH OF CARCINOMA CELLS WITHIN THE MUSCLE FIBRES IN CARCINOMATOUS METASTASES TO VOLUNTARY MUSCLE.

BY G. HOWARD WHITE, M. D.

(From the Ayer Clinical Laboratory of the Pennsylvania Hospital, Philadelphia.)

In the histological examination of a carcinoma of the mammary gland, it was noted that about the margins of a metastatic nodule situated in the pectoralis major muscle the carcinoma cells appeared to be within the muscle fibres, surrounded by sarcolemma and replacing the sarcoplasma. To determine the frequency of this condition and the method by which the cells entered the muscle fibres, a study was made of all the carcinomatous metastases to voluntary muscle which could be obtained; and the present paper embodies the results of this study.

The early observations on carcinoma of muscle are closely connected with the question of the specificity of tissues, and one finds in the literature many discussions as to whether muscle cells can give rise to carcinoma, either as a primary or secondary growth; and whether the sarcolemma or the connective tissue of the muscle can be considered as the point of origin of the growth.

The earliest article found was one by Chevalier in 1826, who said that carcinoma invaded muscle by insinuating its gristly sprouts between the muscle fasciculi—retracted these into its substance—and caused them by pressure or by absorption to lose their fibrous or muscular character; while sarcoma, he said, engulfed the muscle but the muscle fasciculi preserved their character better and could be traced through the tumor pulp. Walshe considered that the cancer was primary in "the cellular membrane separating the fasciculi of muscle fibres" and stated that the muscle was transformed into an "encephaloid structure" though the form of the fibres was retained. Bennett made microscopic examinations of carcinoma of muscle but had not apparently in 1849 discovered carcinoma cells lying inside the sarcolemma.

In 1848 Lebert saw, in a case of carcinoma of the tongue, carcinoma cells in some of the muscle bundles. Little notice was taken of this observation and after the publication of Schroeder van der Kolk's article[1] describing the same condition, the latter author was usually regarded as the first to have made this observation. Van der Kolk and Lebert both believed the cells to be transformed muscle cells. Following these communications, much interest was shown in the matter. Billroth thought that possibly the muscle cells were changed to carcinoma cells but later decided that the carcinoma arose from the myolemma which he considered as evidence of connective-tissue origin. Böttcher believed that the cells arose from the sarcolemma, and though Weber believed that most of the cells arose in this manner he also contended that some arose from the muscle nuclei. Kölliker adopted the view of the origin from muscle tissue.

Virchow stated that the cells arose not in the muscle fibres or the sarcolemma, but in the connective tissue, and later penetrated the sarcolemma. Neumann a year later repeated this view, and said that he had seen sections which showed that the growth spread from only one point in the sarcoplasma, a fact which he considered was in favor of the view that the process was an invasion of the mucle fibres and not a transformation of muscle cells into tumor cells.

Förster's opinion seems to have varied. In 1863 he upheld the theory of origin from connective tissue, but believed that "secondary carcinoma" could sometimes arise from the muscle cells. Sick considered that the origin of the cells was in the capillaries of the muscle. Popper said that carcinoma could arise both from connective tissue and from muscular tissue interchangeably.

Waldeyer's article in 1867 was the first on carcinoma of muscle which advocated his now universally accepted view that the growth must arise from epithelial cells elsewhere. He admitted that there was a proliferation of the nuclei of the muscle but insisted that these nuclei could not produce carcinoma cells. At this time he believed that the tumors were metastases carried to the muscle by way either of lymph- or blood-vessels.

Volkmann described sections showing the openings through which the carcinoma cells entered the sarcolemma but thought that the primary point of origin was the connective tissue.

The only statement which could be found from America concerning this question is an incidental sentence in a lecture by Woodward, where he emphasizes the presence of a small round cell infiltration and suggests that it may have given rise to the idea that the proliferation of the muscle nuclei may produce carcinoma cells.

The later articles of Schaeffer and Christiani treat the subject from a modern point of view, and Cornil and Ranvier have an excellent article in the last edition of their "Manuel d'Histologie Pathologuique," in which they desribe the occasional occurrence of carcinoma cells within the muscle fibres of voluntary muscle, the seat of carcinomatous metastases.

A search of the literature for any definite information concerning the lymph vessels of muscle was unfruitful. The usual statement is that they exist only in the connective tissue and accompany the blood-vessels. Sappey says that the main trunks in the muscle itself run parallel to the muscle bundles, and give off many branches forming anastomoses with the neighboring trunks. An attempt made in the laboratory to inject and demonstrate lymph vessels in muscle was unsuccessful. The material which was studied consisted of tissue from six cases of carcinoma of the breast with involvement of the pectoral muscles. Zenker's fluid was used as a fixative. Sections were cut in paraffin and stained with hæmatoxylin and eosin. One serial set of 115 sections was obtained through a small metastasis in the pectoral muscle. These were cut transversely to the muscle fibres. Much the same mode of growth was seen in all the cases.

Sections through an area of advanced tumor growth show nests of carcinoma cells usually with a large proportion of fibrous tissue between; and no vestige of the original muscle can be found. Sections of a less advanced stage show, however, a striking persistence of the arrangement of muscle fibres. In sections cut transversely to the muscle bundles and studied under the low power one finds rounded masses of cells corresponding to the muscle bundles and giving at first glance an appearance much like that of a gland; while on longitudinal section one sees elongated cellular masses stretching across the field.

The reaction on the part of the muscle is shown by a small round-cell infiltration which may be intense or almost entirely lacking, and by a marked degree of interstitial myositis. The cross striation is preserved until the muscle is markedly involved in the tumor growth. The nuclei are almost always increased in number, often forming lines in longitudinal

[1] Content known only through references in the literature.

sections. The sarcoplasma appears granular, and takes the stain irregularly, giving the impression of rifts in the protoplasm. In some bundles, especially in the portion nearest the epithelial cells, the sarcoplasma shows a hyaline degeneration and stains very deeply in eosin.

On closer examination of the cross-sections under the high power, one finds, particularly about the margins of the metastases, small masses of carcinoma cells lying in the muscle bundles among the muscle fibres. Some are quite round and are seen to be surrounded by a delicate membrane. These do not lie between the muscle fibres but are in a position which corresponds exactly to a muscle fibre itself (see Fig. 1, C). Often it can be made out that this delicate membrane is really the sarcolemma of a muscle fibre, for in some cases a little sarcoplasma is present beneath the apparently intact sarcolemma (Fig. 1, A), separating it from the collection of carcinoma cells. This sarcoplasma may form a crescent or a half-moon on one side of the carcinoma cells (Fig. 1, D and E), or sometimes a ring surrounding one or more cells; occasionally one sees a single cell lying just beneath the sarcolemma in an indentation in the sarcoplasma. Between the fasciculi of muscle bundles one sees carcinoma cells lying in the lymphatics which surround the blood-vessels in these situations (Fig. 1, B).

Longitudinal sections show a corresponding picture (Fig. 3). The carcinomatous tissue occupies the sarcolemmata with some or no sarcoplasma along its edge. One can occasionally find bundles showing how the carcinomatous and muscular tissue dovetail into one another inside the sarcolemma, giving the picture in the cross-section of a fibre half filled with carcinoma cells. Here, too, there are strands of cells which cannot be shown to be within the sarcolemma but which lie in the perivascular lymphatics of the connective tissue.

Serial Sections.—One end of the series is in a dense tumor growth, and at the other end, in certain parts of the sections, the epithelial cells have almost entirely disappeared. Starting from the portion where the growth is most developed and following the sections toward the advancing edge of the metastasis, one finds that the masses of cells grow smaller and more discrete until they come to occupy only the spaces within the sarcolemmata with no free tumor cells near them. One can trace very clearly all the stages of transition from the round nests of epithelial cells to the perfect muscle fibre (Fig. 2). Following up any one muscle bundle the epithelial cells will be found to show first a thin border of sarcoplasma, at one side or perhaps surrounding them; then the area of the epithelial cells gradually decreases with a proportional increase in the area of the sarcoplasma. This decrease in the number of epithelial cells is not always steady, but may cease for a few sections or there may even be a slight and transitory increase. Further on one finds only one or two epithelial cells lying either in the central or peripheral part of the sarcoplasma (Fig. 2, A), and finally the carcinoma cells disappear entirely, leaving a perfect muscle bundle.

No bundles were found containing epithelial cells in which it was not possible to trace these cells to a point where the bundles were lost in dense carcinomatous growth. That is to say, no islands of carcinoma cells were found isolated from the main growth.

The deep red hyaline appearance of the muscle fibres in the neighborhood of the tumor cells is very well marked in these sections, and on tracing the sections toward the carcinoma one can tell by the change in appearance of a bundle that epithelial cells are present within its sarcolemma before one sees the cells themselves, and can foretell that they will appear a few sections further on.

From a study particularly of serial sections it seems possible to explain the method by which the carcinomatous growth penetrates the muscle fibres. The carcinoma cells evidently reach the muscle through the lymph vessels supplying the muscle; since the lymph vessels so involved are usually located in the connective tissue between the muscle fasciculi, the original metastasis first starts its growth from this situation. The possibility of a similar involvement of the lymph vessels lying between the muscle bundles—if such exist—cannot so far be excluded.

The carcinoma cells which proliferate in the lymph vessels secondarily involve the fasciculi of the neighboring muscle bundles, destroying in their growth many fibres. In this way it is possible that tumor cells may extend into the broken ends of muscle fibres and develop along the course of the muscle bundle, the sarcolemma acting as a sheath. The sarcoplasma seems to offer a comparatively weak resistance to the carcinoma and permits its rapid advance in a longitudinal direction, whereas the sarcolemma offers a comparatively high resistance to the carcinoma and prevents the lateral spread of carcinoma which exists within it.

The interaction of the low resistance of the sarcoplasma and the high resistance of the sarcolemma, causes the presence of carcinoma cells within the sarcolemma, as can be followed in serial sections, far removed from the point at which the carcinoma entered the muscle bundle; giving an appearance in section of carcinoma cells lying within an apparently intact sarcolemma.

No evidence could be found to support the view that carcinoma cells are carried directly to the sarcoplasma through openings normally present in the sarcolemma, and communicating with the lymph vessels; or through openings which they themselves have made by destruction of the sarcolemma at one point.

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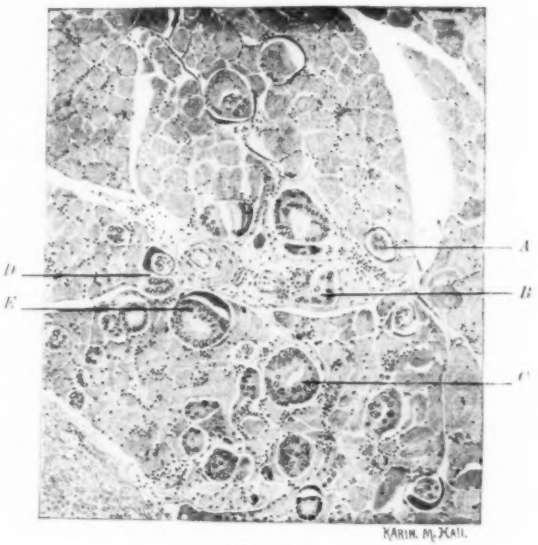

FIG. 1.

FIG. 1.—Cross-section through margin of a carcinomatous metastasis to the pectoral muscles, showing varying grades of replacement of sarcoplasma by carcinoma cells. (Zeiss, oc. No. 4; obj. AA.)

A. Carcinoma cells completely within muscle fibres.

B. Carcinoma cells within perivascular lymphatic.

C. Round mass of carcinoma cells about which no muscle fibres are visible.

D and *E*. Carcinoma cells partially surrounded by muscle fibres.

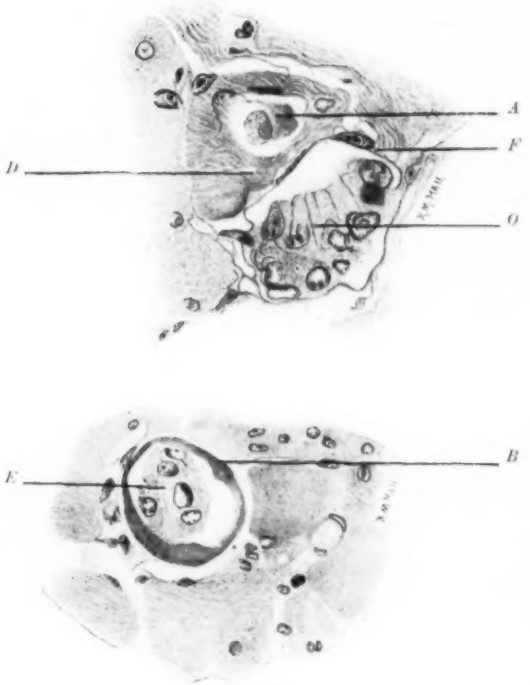

FIG. 2.

FIG. 2.—Tranverse section of muscle fibres, showing varying grades of replacement of sarcoplasma by carcinoma cells. (Zeiss, oc. No. 4; Bausch & Lomb, obj. No. 1/6.)

A O and *E*. Carcinoma cells.

B and *D*. Sarcoplasma. In B, the hyaline appearance of the sarcoplasma is well seen.

F. Delicate membrane surrounding mass of carcinoma cells.

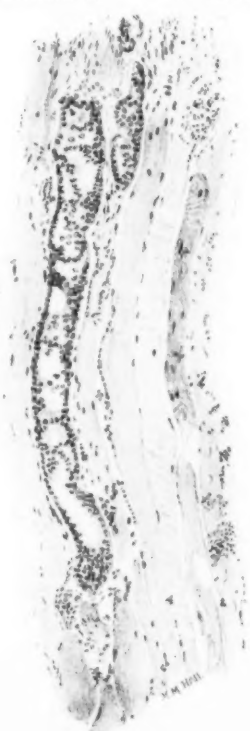

FIG. 3.

FIG. 3.—Longitudinal section through carcinomatous metastasis to pectoral muscle. (Zeiss, oc. No. 4; obj. AA.)

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TYPHOID NODULAR COLITIS.

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The following case seems to be of interest from several points of view; first, in that it is a case of typhoid fever clinically unsuspected, the symptoms being overshadowed by those arising from the disease of the heart valves; secondly, because the intestinal lesions were confined to the colon, and in the third place, because these lesions closely correspond with the description given by Orth and others for the so-called nodular colitis. The following is a very brief outline of the clinical history of this case:

Otto Kast, aged thirty-seven years, German.

Family history, negative.

Past history.—The patient had rheumatism and chorea in his youth; no lues; no typhoid fever. His habits were good. He ran the course of a heart case with mitral stenosis and insufficiently showing frequent breaks in compensation, which caused him to enter the hospital at various times. His last admission was on August 25, 1905, with a bad break in cardiac compensation; he showed marked dyspnœa, edema and cyanosis. There was considerable improvement under treatment. His temperature was constantly subnormal until October 6, when it gradually rose to 101.5° on October 9, where it remained steadily for the greater part of this last illness.

His leucocytes numbered 7,800 on October 8; 9,500 on October 16. During this febrile period he developed signs of pulmonary infarction. He was very restless and uncomfortable, and gradually grew weaker, the weakness being apparently due to his cardiac lesion; was finally delirious the day before death, which took place on October 20. No record was made of any signs pointing to an abdominal complication. The case came to autopsy in the service of Dr. Welch from the medical service of Dr. Barker at the Johns Hopkins Hospital.

Anatomical Diagnosis.—Chronic mitral endocarditis with stenosis; cardiac dilatation and hypertrophy; sclerosis of pulmonary artery; chronic passive congestion of the viscera; localized subcutaneous edema; anæmic infarctions of spleen; hemorrhagic infarctions of lungs; acute bronchitis; broncho-pneumonia; nodular colitis (typhoid); lymphadenitis; old tuberculous foci in lymph glands and lungs; chronic adhesive pleuritis; chronic adhesive peritonitis.

The following is an abstract of the autopsy report: Lower limbs show considerable subcutaneous edema. Abdominal and pleural cavities are clear except for a few old fibrous adhesions. The spleen is adherent to the diaphragm.

Heart weighs 620 grams; there is great distension and hypertrophy of its right side. The pulmonary artery shows several large, opaque, yellow areas of sclerosis, some of which stand fully 1 mm. above the surface. The left auricle is dilated and shows a few sclerotic areas. The mitral orifice shows a typical "button hole" opening which just admits the tip of one's little finger. Aortic and pulmonary valves are delicate. Aorta shows little sclerosis. The coronaries show only an occasional patch of moderate thickening.

Lungs show some old pleural adhesions and one apical scar with a small caseous central focus. Some of the bronchial lymph glands show caseous encapsulated foci.

The bronchi show a deeply injected mucosa of a purplish color. Cut sections show areas of broncho-pneumonia and wedge-shaped infarctions scattered over the elastic, tough, salmon-red-colored lung tissues.

Spleen weighs 450 grams; there is some thickening of the

capsule and tags of old adhesions over it. It is firm and the cut surface is sharp. The trabeculæ are not distinct. The pulp scrapes off on the edge of the knife with difficulty and is of a pale purplish color. The malpaghian bodies are clearly visible as small gray dots. There are several pale, cream-colored infarcts with their bases at the surface, extending some distance into the parenchyma and surrounded by a zone of injection.

Pancreas is normal.

Liver weighs 1,750 grams. It is adherent to the diahpragm by old adhesions, and to the duodenum by pericystic fibrous adhesions. The cut surface is fairly typical of chronic passive congestion.

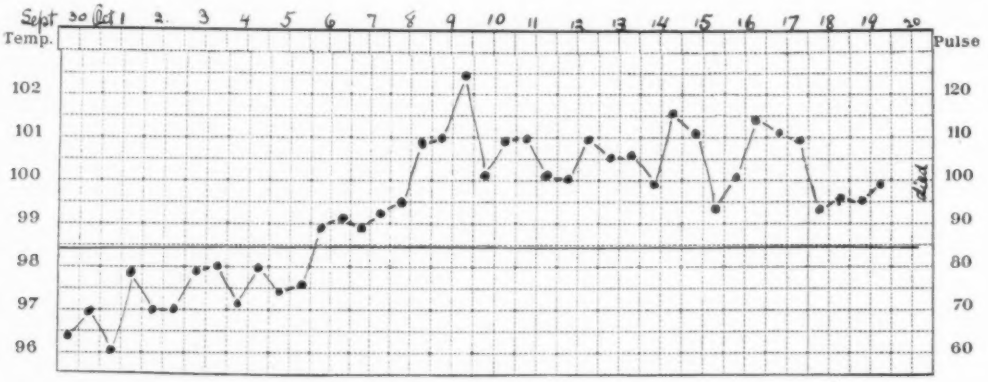
Kidneys weigh 530 grams. Their capsules come off readily and both are fairly typical examples of the kidneys of chronic passive congestion, with some cloudy swelling of the cortex.

Pelvic organs are normal. The mesenteric glands are slightly enlarged, the change being most marked in those glands situated along the transverse and ascending colon.

cular outline: some are quite deep extending down through the thickness of the nodule, but in no instance do they invade the muscularis. The deep ulcers may show some undermining of their edges, and their bases are covered with an adherent, grayish-yellow slough. The solitary follicles are visible in this area and were described as the earliest stage in the formation of the nodules.

The ascending and transverse colon show much the same appearance, except for the fact that the nodules are more thickly placed, and in some areas as many as ten or twelve can be made out in a space measuring 3x3 cm. The transverse colon shows some enlargement of the solitary follicles up to 1 mm. in diameter, these being evenly distributed over the mucosa between the larger ulcerated nodules. The descending colon and sigmoid show fewer of the larger ulcerated nodules as one approaches the rectum, but the smaller nodules are quite numerous in this region.

Rectum shows intense injection, giving its mucosa a deep, purplish color, but no nodules.



Some of the larger ones measure 1.5 cm. in diameter, and cut section shows scattered areas of focal necrosis on a translucent background.

Digestive Tract.—Stomach is normal. The upper part of the duodenum shows some injection and a pinkish smooth mucosa. The jejunum and ileum are normal, showing a pale, pinkish mucosa. The lower portion of the ileum was preserved in formalin together with the cæcum, appendix and ascending colon. This specimen shows not the slightest swelling of the Peyer's patches, or solitary follicles in the ileum.

The appendix is thick and short, but free from adhesions. Its lumen is patent for only 2 cm. from its junction with the cæcum, but there is no evidence of any ulceration or swelling of its lymphatic tissue. The ileo-cæcal valve is normal.

The mucous surface of the cæcum is thickly sown with small sessile nodules from 2 to 10 mm. in diameter, in some instances projecting 4 mm. above the surface. The larger nodules show small round ulcers on their crests, but elsewhere the mucosa is intact and of a pale purplish color. The ulcers vary from very minute dots to areas 5 mm. in diameter. The majority of them are superficial with a clean cut edge and cir-

At the time of autopsy there was not the slightest suspicion that the lesion was due to the typhoid bacillus, and it is very unfortunate that no cultures were made from the intestinal lesions, spleen and glands. The culture from the heart's blood was sterile.

Microscopical Specimens.

The Intestinal Lesions.—Small intestine shows a perfectly normal mucosa. The Peyer's patches and solitary follicles do not show any hyperplasia, and the submucosa is normal except for a marked degree of chronic passive congestion. The appendix is negative.

Large Intestine.—The mucosa except over the larger nodules is normal. The solitary follicles, which were quite conspicuous in the transverse colon, show little, if any, hyperplasia but in some instances seem raised above the surface and rendered prominent by an infiltration of the submucous stroma with wandering cells of various types, some of which are phagocytic. In such areas too there is a certain amount of edema of the stroma and injection of the capillaries. Several of the nodules from different parts of the intestines, measur-

ing 2 to 5 mm. in diameter and showing no superficial ulceration, were cut in serial sections and stained with polychrome methylene blue and eosin or haematoxylin and eosin. Such nodules usually contained one or two solitary follicles which might be located at the summit of the nodule or on one side, never in the centre of the nodule. These solitary follicles showed no hyperplasia as a rule, but one or two which occurred in the stroma of a nodule showed a little edema and infiltration with epithelioid cells, maintaining sharply their independence however from the main bulk of the nodule. Some follicles in the mucosa near the nodules are perfectly normal and show absolutely no evidence of any hyperplasia. The nodules themselves appear to be made up of an edematous stroma infiltrated uniformly with numbers of lymphoid cells and a few leucocytes. The predominating cells, however, are large, oval, "epithelioid" cells with eccentric nuclei, often phagocytic and showing a variety of granules. There are many cells which correspond to the "polyblasts" of Maximow. The capillaries in the nodules are always dilated and some of the smaller ones as well as many lymph sinuses are packed with phagocytic epithelioid cells. These nodules all show scattered focal areas of necrosis with fragmented nuclei, usually of small size but sometimes conglomerate and containing clumps of pale-staining, slender bacilli. The larger ulcerated nodules, averaging from 5 to 10 mm., show a typical picture of typhoid hyperplasia in the submucosa round the ulceration, the loose edematous stroma being packed with large, oval, flat epithelioid cells which are actively phagocytic. There are many round cells and polyblasts of all kinds but few leucocytes. Solitary follicles are seen in these areas, sometimes on the shoulder of a large nodule, maintaining its normal appearance and showing absolutely no change, and again at the edge of a nodule but unchanged as a rule and taking no active part in the reaction. A few follicles are found which show a little edema and invasion with epithelioid cells, but only to a limited degreee.

The ulceration in some cases seems to extend from the surface, due to anæmia of the mucosa consequent on its stretching over a large nodule. More commonly the ulceration merely connects a large area of focal necrosis in the middle of the nodule with the lumen of the bowel, in many such cases the ulcer being very small with extension of the necrosis under the overlying intact edges of mucosa. Gram-staining micrococci are found in the edges of the ulcers, but no gram-staining organisms in any other tissues. No acid fast bacilli were demonstrated in any sections. Large areas of focal necrosis are usually present and appear to be formed by fusion of the smaller foci seen in the smaller nodules. Strands of fibrin are interwoven with these focal areas and connect them to each other, interlacing with strands of fibrous tissue (as is sharply brought out by Mallory's connective tissue stain). The meshes of fibrin are full of the wandering cells, described above, with many fragments of nuclei and leucocytes in the more central portions of the necrotic areas and in the bases of the ulcers. Some of the smaller vessels in and near such areas are thrombosed. Beneath some of the larger nodules the internal muscular coat shows some injection of its capillaries, edema and separation of the muscle cells with slight infiltration of round cells and a delicate tracery of fibrin.

The mesenteric glands near the cæcum and transverse colon were cut in serial sections and stained with polychrome methylene blue and eosin. They all show a typical picture of typhoid lymphadenitis with numerous small scattered areas of focal necrosis and infiltration of the lymph sinuses with phagocytic epithelioid cells. Numerous large clumps of bacilli are found. The capillaries are congested.

Liver sections show advanced chronic passive congestion of the lobules and some fatty degeneration. Scattered areas of focal necrosis are found similar to those seen in typhoid fever.

Spleen sections show chronic passive congestion and a few scattered phagocytic cells like those described in the lymph glands. The most characteristic thing is the finding of large clumps of bacilli in the pulp. These organisms decolorized by Gram and stained clearly but not deeply by polychrome methylene blue and eosin. They always occurred in large clumps as is so characteristic of the typhoid bacillus in this organ. Studied with a one-twelfth objective the organisms appear as slender bacilli and correspond exactly in morphology to the typhoid bacillus. Exactly similar organisms are found in large clumps in the base of the intestinal nodules, mesenteric lymph glands and liver. The spleen also shows several fresh anæmic infarcts with a halo of leucocytes and hemorrhage. Some sections show focal necroses in the malpighian bodies.

Kidneys show congestion of the capillaries everywhere, especially in the glomeruli, and marked cloudy swelling of the secreting structures of the cortex.

Lungs show advanced chronic passive congestion with scattered areas of red infarction and bronchopneumonia. There is an old tuberculous focus with a thick fibrous capsule.

The other organs are negative.

Lesions in the large intestine, which give a similar picture, are not infrequently found in typhoid fever cases, but associated with swelling and ulceration of the lymphatic apparatus of the ileum. Woodward reports a case (No. 882, Med. History of the War of the Rebellion, Part II, page 360). A man dead of a severe attack of typhoid fever showed at autopsy a colon which presented a remarkable picture of nodular swelling with superficial ulceration. The illustration of this case is almost an exact duplicate of a portion of the colon in this case. He says that the nodules are due to hyperplasia and ulceration of the solitary follicles, but gives no microscopic report. The small intestines showed a remarkable hyperplasia of Peyer's patches and follicles. In a previous case of typhoid fever in this hospital (autopsy 1435) the mucosa of the colon was dotted over with nodules of various sizes up to 10 mm. in diameter, showing in places slight superficial ulceration. The small intestine showed extreme hyperplasia of the lymphatic tissue. Microscopic

examination of these nodules showed a picture corresponding fairly closely with the lesion in the nodules described above. The bulk of the nodules was made up of an edematous stroma packed with large flat, epithelioid cells, which were very actively phagocytic. Several lymphoid follicles occurred in all the large nodules and preserved their integrity, although a little swollen and infiltrated by many of the large wandering cells. It was quite evident that the nodules were not due to hyperplasia of any one or of several lymphoid follicles, which formed only a small fraction of these nodules. Focal necroses were seen, but widely scattered and of small size. Ulceration was slight and very superficial, extending scarcely beyond the muscularis mucosæ. Clumps of bacilli were seen in the stroma of the nodules which coresponded in morphology to the typhoid organism. Cultures from various organs showed growth of *B. typhosus*.

Typhoid ulceration confined to the large intestine, the colotyphus of the French writers, was not thought to be exceptionally rare before the literature was looked over in pursuit of such cases. Many of the larger text books of Pathology make no mention of such cases. Nothnagel as well as Brouardel and Thoinot (La Fièvre Typhoide) state that "colotyphus" is extremely rare. Hoffmann[1] in a study of 250 cases at Basel only reports one case, as follows:

Male twenty-five years old.

The patient came in with high fever and soon became delirious. He later developed a purulent discharge from both ears. Shortly before death on the forty-second day of his illness the sputum became purulent and foul-smelling with other signs of pulmonary complications.

Autopsy: Chest.—The left pleural cavity contained 200 cc. of thin, clear, yellow fluid. Heart was normal. Lungs showed acute bronchitis and perhaps bronchiectasis or gangrene.

Abdomen.—The stomach was enlarged and showed a few submucous ecchymoses near the fundus. The intestines were distended with gas. The small intestine showed no swelling or ulceration throughout its course. There were a few ecchymoses near the ileocæcal valve. In the cæcum, ascending and transverse colon the follicles were swollen, and some of them show ulceration of slight extent but yet extending to some depth, even to the muscularis in some instances. Several of the ulcers were covered by a thin delicate membrane whose margins are pigmented and of a grayish color. The mesenteric lymph glands were scarcely enlarged and of a dark, grayish-red color. The liver was very large and cut section of a pale, grayish-yellow color. The spleen measured 16.5 cm. in length, capsule wrinkled, parenchyma soft, pulpy and of a purplish color. The kidneys showed a "horseshoe" malformation with firmly adherent capsule and cloudy cortex. Brain was negative, middle ear findings not relative.

[1] Untersuchungen über die pathologisch anatomischen Veränderungen der Organe beim Abdominaltyphus, 1869, Von C. E. E. Hoffmann.

Marchand[2] reports a case of a young man clinically one of severe Typhoid Fever. Autopsy showed intestinal lesions limited to swelling and superficial ulceration of the solitary follicles of the large intestine. The spleen was greatly enlarged and the cut section studied with grayish-red enlarged malpighian bodies, which at first sight suggested tubercles. He considered this appearance to be due to active hyperplasia of the malpighian bodies with comparative escape of the spleen pulp. The mesenteric glands were enlarged and showed on section little pale dots in the parenchyma which microscopically were small areas of necrosis. Most of his paper was devoted to a discussion of the method of formation of the sloughs in typhoid ulceration.

Hodenpyl[3] reports a case at the Roosevelt Hospital of a man thirty-one years old, who ran a typical course of typhoid fever. Autopsy showed a small intestine which was entirely normal. The colon, except the sigmoid and rectum, was studded with ulcers from 2 to 15 mm. in diameter, having sharp edges and a circular outline. Cultures from the spleen showed *B. typhosus*. Microscopical sections showed hyperplasia at the margins of the intestinal lesions and focal necroses in the liver. The small intestine showed no hyperplasia of the lymphoid elements. The spleen and mesenteric glands were not examined.

In looking over the available literature on the subject these three cases were the only ones found which were satisfactorily reported. Doubtless cases have been mentioned in reports on other lesions, as in Marchand's case, which have escaped our notice, but it may be stated with some certainty that typhoid intestinal lesions limited to the large bowel are very rare. The case reported from this laboratory is the only one in a series of 217. It is unfortunate that in this case no cultures were taken from the spleen and other organs, but the microscopic picture of the intestinal lesions and mesenteric lymph glands, together with the finding of typical clumps of bacilli in the spleen and mesenteric glands seems to leave no doubt that this was a case of typhoid fever. A review of the clinical history shows a temperature curve and leucocyte count which support this conclusion.

The term "nodular colitis" was used in this instance because it seemed to fit exactly and accurately describe the lesion. The terms "enteritis nodularis" or "enteritis nodularis hyperplastica" seem to have been introduced by Orth, who described these lesions in cholera, diphtheria, typhus and typhoid fevers. The illustration which is found in his book was taken from a case of cholera and resembles this case very closely, but he describes the lesion as due to a hyperplasia of the solitary follicles with central softening and ulceration. He classifies the lesion under Infectious Granulomata.

Rokitansky seems to have confused several kinds of ulcers of the large intestine. He describes an increase in size of the

[2] Centralblatt für Allgemeine Path. u. Path. Anatomie, 1890, I—121.

[3] Brit. Med. Journal, 1897, II, pp. 1850.

solitary follicles going on to central softening with ulcer formation, but says that these ulcers may undermine the mucosa, coalesce with one another and finally lay bare large areas of the muscular coat. The last part of his description is suggestive of amebic ulceration.

Ziegler describes enteritis follicularis as consisting of marked swelling of the lymph nodules and Peyer's patches, which may go on to central softening and ulceration. There may be any type of associated enteritis. He does not use the term "enteritis nodularis," nor does Nothnagel refer to it. The latter uses the term "follicular ulceration" and says that it is more common in the large than in the small intestine; further, that the ulcers are commonly of small diameter but may extend through the muscular coats and even perforate. Histologically the lesion consists of a great accummulation of wandering cells in the submucosa and solitary follicles. The mucosa on the summit of the nodule undergoes a pressure necrosis and the ulcer grows from the surface.

Bamberger[4] confused follicular ulceration and chronic cystic colitis in that he considered the small cysts, full of mucus and formed from dilated glands, to be small abscesses in the solitary follicles.

Virchow[5] calls attention to this error and states that this type of follicular ulceration can be confused with colotyphus as there are many points of similarity. However, the follicular ulceration is preceded by abscesses in the follicles which rupture through a *small* opening, thus forming a tiny ulcer. On the other hand, the typhoid ulceration of the swollen follicles is not cavernous and undermined with a punctate opening, but superficial and having more of a ring shape with no evidence of abscess formation, or suppuration.

Woodward described the specimen from the case cited above as "Transverse Colon with Enlarged Glands Ulcerated at their Apices." He states that he places this case, not in the typhoid section where it would seem to belong logically, but in the section on ulcerations of the colon, because it differs only in *degree* from similar enlargements of the solitary glands found in cases of simple acute diarrhœa. He pictures numerous types of such enlargement of the follicles in diarrhœa and describes a "follicular ulceration." He says the first step consists of an enlargement of the solitary follicles by accumulation of cells from the blood or by proliferation of the fixed cells. Ulceration may take place in quite small as well as large follicles by two methods, either by central softening and surface rupture or by a superficial loss of mucosa and extension downward. These ulcers are described as circular in outline, with undermined, overhanging edges. More or less inflammatory reaction is always present in such areas, giving a cellular infiltration of the submucosa as well as the underlying muscular coats. According to Woodward the process always begins in a follicle and results in its destruction, if ulceration occurs. Once started the ulceration may involve the infiltrated submucosa and even the underlying coats.

This short review of the subject of enteritis nodularis, follicularis, etc., shows how varied is the nomenclature regarding the inflammation or hyperplasia affecting the lymphatic tissue of the large intestine. It would seem that no writer has called attention to the difference existing between the cases of follicular or lymphatic hyperplasia of the intestine, which are so commonly seen in children dead from any acute intoxication (for example diphtheria) and the class of cases described in this paper and pictured by Orth, Woodward and others.

The term lymphatic hyperplasia is used in this laboratory to designate cases showing swelling of the lymphatic tissue of large or small intestines. This lesion is most common in children dying from some acute infection when the large intestine may show nodules up to 2 mm. in diameter sometimes with superficial ulceration. These nodules, however, are evenly distributed over the mucosa and correspond in number and distribution to the solitary follicles. Histologically each nodule consists of a solitary follicle, which may show some edema and infiltration with wandering cells, but chiefly a simple hyperplasia. The submucosa is usually quite normal, but may show a moderate degree of congestion of its capillaries.

The term nodular colitis should not be confused with that of lymphatic hyperplasia, for in the former case the solitary follicles would seem to play only an unimportant role and form a small fraction of the nodules which, as described above, are made up of an edematous stroma infiltrated with various types of polyblasts or wandering cells. The nodules are dotted over the colon in a haphazard fashion with no fixed relation to the follicles and are as a rule larger than those seen in lymphatic hyperplasia. This lesion appears to be found most frequently in cases of typhoid fever, but at best is quite rare, whereas lymphatic hyperplasia is common in children and not infrequent in adults. Probably the lesion can be produced by a variety of organisms, for example, those of cholera and typhoid, and may be classed (Orth) under the infectious granulomata.

SUMMARY.

1. Typhoid intestinal lesions limited to the colon are very rare.

2. The term "nodular colitis" should be restricted to such cases as show a marked infiltration of the submucosa with wandering cells, giving rise to prominent isolated nodules having no relation to the solitary follicles which are comparatively unaffected. These cases are of rare occurrence.

3. The term "lymphatic hyperplasia" may be used to describe the cases showing a simple hyperplasia of the solitary follicles of the intestines and a relatively normal submucosa. These cases are commonly found at autopsy.

[4] Virch. Handbuch der Spec. Path. und Ther., 1864, VI, 1—356.
[5] Virch. Archiv., 52, p. 22, "Kriegstyphus und Ruhr."

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY,

May 21, 1906.

A Simple Method for the Quantitative Determination of Proteid in Milk. DR. BOGGS.

Dr. Boggs presented a new, simple method for the quantitative determination of proteids in milk. This will be published in full in a future number of the BULLETIN.

He also exhibited two unusual malarial specimens obtained from the blood of a patient. These specimens represent the parthenogenetic division or development of the organism as described by Schaudinn in explanation of the recrudescence. The female form persists after the others have died out and throws out a polar body-like structure followed by a division of the nucleus unequally, which is in turn followed by a division of the protoplasm. Eventually a number of spore bodies are formed similar to the merozoites of the asexual cycle.

The Blood in Pernicious Anæmia. DR. EMERSON.

I wish to call attention to certain points in the blood of patients with pernicious anæmia which we have noted in the cases admitted to the wards during the past five years.

First, the blood on admission shows a higher average count (about 1,500,000) than in other clinics, and I believe this is due to the fact that cases are admitted for other than the condition of the blood itself—the nervous manifestations of the disease for example.

Secondly, there is quite frequently a non-parallelism between the blood count and the patient's condition. The patient will enter with a certain count, feeling badly, and will leave later with exactly the same count though he feels well. In another group illustrating this same fact the count will rise steadily though the patient dies. In still another group there is a rise, then a fall to about the first count and the death of the patient then occurs. This rise and fall is of interest. With a 50,000 variation in the count per day this is often not due to the new formation or destruction of the red blood corpuscles but to changes in the concentration of the plasma, changes which are greater in this disease than in any other. A rise, however, of from 15,000 to 20,000 cells per day may mean a new production of corpuscles as these rises are often accompanied by an increase in the leucocytes and eosinophiles which shows bone marrow activity.

In a certain number of cases with a count of from 300,000 to 700,000 cells at the time of death, death appeared to have resulted from the anæmia alone as there were no complications. This seems to be the average count at the time of death from the anæmia alone.

Megaloblasts—and by this term I mean a large nucleated red blood cell the nucleus of which is about the size of a normal erythrocyte, all with smaller nuclei being considered as intermediate forms—are of considerable interest. The reason for the line of division given is as follows. The marrow of an infant or of a case operated on for empyema shows two groups of cells, one with a large nucleus, the megaloblast described above, and secondly a red cell with a smaller nucleus. We suppose the larger cells represent the centers of the islands for proliferation of the red blood cells and after the outer zone of normoblasts is stripped off in this disease, pernicious anæmia, these float out, and are the megoblasts.

The line drawn here in this clinic for a crisis is the finding of 50 nucleated red blood cells per 1000 leucocytes, and fully one-half of the crises do not result in a gain in the red cells. There are two kinds of crises, normoblastic and megaloblastic, and the latter seem the last efforts of the marrow, often unavailing.

A color index of over 1½ is open to criticism. The color index in this disease is high for, (a) the large size of the cells, though the color of the cells at times seems to indicate an increase in iron content, though this is probably not any higher than normal, (b) large numbers of microcytes, (c) the most important factor is the poor instrument used, and our high indices are due to the v. Fleischl instrument.

The leucocytes in pernicious anæmia are interesting. As a rule they vary directly with the red corpuscles, rising and falling with them. In many of these variations the percentage of the leucocytes remains the same. Cases with a leucocytosis usually have some complication.

In considering the percentages of the leucocytes a thing to be emphasized is the finding of say 60 per cent of small mononuclears. This does not mean a lymphocytosis as the absolute, rather than the relative count, must always be considered. In only 17 per cent of all our cases has there been a true lymphocytosis.

The last point I wish to emphasize is the count of the eosinophiles, not the percentage, as this cannot amount to much, but the absolute count. If these cells are rising the case is improving, and if they are decreasing the opposite is true. This is well shown by a case with a count of 2,700,000 cells right along during the stay in the hospital. During this time the eosinophiles were steadily dropping and reached zero at the time of the patient's death. Even with a rising red blood count the falling eosinophiles tells of the approach of death.

INDEX TO VOLUMES 1-16 OF BULLETIN.

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NOTES ON NEW BOOKS.

Materia Medica and Therapeutics. By J. MITCHELL BRUCE, M. A., LL.D. (Hon.), Aberd., M. D. Lond. (*Chicago: W. T. Keener & Co., 1906.*)

A Manual of Medical Treatment or Clinical Therapeutics. By I. BURNEY YEO, M. D., F. R. C. P. (*Chicago: W. T. Keener & Co.*)

In these recent editions of English works on Therapeutics the formulæ has been adapted to the American Pharmacopeia by Oscar Oldberg of Chicago. In both the apothecary weights and measures only are used, which seems unfortunate, as the metric might well be added. These works differ widely in scope and perhaps that of Dr. Bruce's may be regarded as more adapted for the student who has his materia medica to learn and finds it easy to pick up some therapeutics with it, while that of Dr. Yeo is more for the final student or graduate.

The arrangement of Bruce's work is excellent. After the introduction dealing with preparations, weights and measures, etc., comes the discussion of the inorganic and organic materia medica. The arrangement here is good and may well be commended. The various preparations are given, with concise notes as to their preparation, solubility and dosage. These are complete and put in very concise form. Following this is a section on their action and uses, first the external and then the internal action being given. The drug is followed through the body and its action in excretion, if there be any, is noted. Then there is a brief summing up of the uses of the various preparations of the drug. By this method we think Bruce has perhaps the best section in the action of drugs of any text-book, certainly there is none in which the student can get such a clear idea of the action of a drug and its preparations. The work which enables the student to learn something of the use and purpose of drugs at the same time as the details of preparation and dosage are being gained, has certainly a great advantage.

The latter part of the book deals with general therapeutics and this is necessarily much condensed. In each section the general physiology, the pharmacodynamics, the pathological relations, natural prevention, and recovery, and lastly therapeutics are discussed. We are glad to see that Dr. Bruce does not consider drug giving to be the sole aim of therapeutics. Throughout this section the treatment advised is rational and sound. The work as a whole is excellent and compact. One criticism might be made on the character of the printing. This is poor and the type is not an easy one to read. It is to be hoped that this will be improved in later editions.

Turning to Yeo's book, the reviewer finds it much more difficult to express an opinion. It deals with treatment solely: there is no materia medica. It contains more than therapeutics, for many times the author wanders from the field of treatment into that of general medicine. Much space is given to the discussion of symptoms which doubtless in some ways is a help to the later discussion of treatment. The book is well written and one has no special objection to reviewing symptoms again, but it is doubtful if this is quite the province of a work on treatment. Certainly the discussion of methods of diagnosis—*e. g.*, in stomach diseases—must be regarded as out of place in this work. There are sections given to the treatment of symptoms which are valuable, if they do not lead the student to be too content with the handling of these and so less likely to strive for the solution of the essential causal condition. Yet we are likely to have to continue to treat symptoms.

In the matter of treatment there are many minds and there may be various methods of aiding a patient to get well, but it seems in some things Dr. Yeo hardly holds what may be considered the best modern views. Take the treatment of pleurisy with effusion for example. That early and repeated tapping is the best treatment seems well established, and yet Dr. Yeo advises against this except in the case of large effusions. In moderate effusions he says "we should, however, be in no haste to advise paracentesis." Leave out the *no* and we should agree with him. In the treatment of typhoid fever, Dr. Yeo of course advocates his chlorine water. As a young house officer, the reviewer, full of therapeutic hopefulness, tried it with a number of patients, but the expected results as given by Dr. Yeo were conspicuously absent. To those of us who know the Brand treatment, the reference to it here must be irritating. If many of those who write on it would take the pains to inform themselves accurately on the method and what is hoped for by its use, there would be fewer such comments as we see here. Dr. Yeo is right when he says it involves trouble, but is that not a cheap price to pay for six to eight patients saved in every hundred? To suggest that the bath treatment is especially to reduce pyrexia shows that the author does not understand it. It seems to be a Britannic idea that the bath treatment must be used only for desperate conditions which is fair neither to the patient nor to the method. The administration of gallic acid for intestinal hæmorrhage cannot be commended.

While comment has been made on some points which might be improved, yet the greater part of the work is excellent. It has the advantage of making one think of the reasons for given procedures and that is a desirable feature. Measures, other than drugs, receive proper consideration, in which particular many of the works on therapeutics are conspicuously lacking.

Refraction, Including Muscular Imbalance and the Adjustment of Glasses. By ROYAL S. COPELAND, A. M., M. D., Professor in the University of Michigan, and ADOLPH E. IBERSHOFF, M. D., Instructor in the University of Michigan. (*Philadelphia: Boericke & Tafel, 1906.*)

We believe that this treatise on refraction will be found especially useful to those who are about to take up the practice of ophthalmology. The word practice is used advisedly, for the work is thoroughly practical, as any treatise on this subject to be a real help to an ophthalmologist should be. It is free of technicalities and consequently does not demand that we refresh our minds with the significance of mathematical formulæ and terms. The illustrations of the myopic, hyperopic, and astigmatic eye and of the effect of the correcting lens upon each of these conditions are excellent. The experience of the authors, however, is certainly at variance with that of the reviewer in that they "succeed in coaxing out the most obstinate accommodation and accurately measuring the degree of eye-strain without the use of a cycloplegic, the latter being necessary in exceptional cases only." The longer we treat this class of cases the more we are convinced of the importance of knowing what the eye shows with a paralyzed accommodation. There is nothing more uncertain than the behavior of a ciliary muscle and we are surprised to find how often this is true after thirty-five, from which age on, according to the authors, cycloplegics are rarely necessary because spasm of the accommodation is very rare. We cannot help thinking that the sentiments which bear upon the value of cycloplegics, will be differently expressed in the next edition of the work. The instructions as to the correction of myopia are too meager to be of much help. But what is useful in the book outweighs its shortcomings and we recommend it as a reliable and interesting introduction to the applied principles of refraction.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by A. O. J. KELLY, M. D., Philadelphia, U. S. A., assisted by a corps of collaborators. Vol. IV. Fifteenth Series, 1906. (*Philadelphia and London: J. B. Lippincott Company, 1906.*)

These papers are all interesting, but of unequal value. The best are those which relate to practical topics or present the results of actual clinical experience. Among these in the present volume are Gwyn's "Treatment of Some Common Gastric Disorders," Deaver's "Results of Operations Such as Gastroenterostomy, Pyloroplasty, etc., in the treatment of Diseases of the Stomach," Freiberg's "Study of the Clinical Course of Joint Tuberculosis by Means of the X-Rays." Of the remaining papers some are sketchy and others are profound; while several of them seem to have been written to bring forward a single special feature of a disease or a feature in operative technique. Occasionally the impression is left upon the mind of the reader that the article was written perfunctorily in response to an urgent request for a paper, without special preparation or investigation. And yet there are many excellent monographs upon special topics which give evidence of careful painstaking preparation and subsequent elaboration, such as Brown's "Thyroid Gland," Craig's "Symptomatology and Diagnosis of Malta Fever," and Warthin's "Experimental Study of the Effects of Röntgen Rays Upon the Blood-forming Organs." The book as a whole is valuable and can be commended to the medical profession. The clinical lecture form which characterizes most of the papers renders the style easy and readable. The volume is fully equal to its predecessors.

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